PSJ2 Exh 43

Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 2 of 110. PageID #: 400476 NDA

Purdue Pharma L.S.

100 CONNECTICUT AVENUE, NORWALK, CONNECTICUT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

January 11, 1996

RESPONSE TO PROMOTIONAL QUESTIONS

TWO COPIES SUBMITTED
UNDER SEPARATE COVER
TO ANESTHETIC/CRITICAL
CARE & ABUSE DRUGS

Diane Schnitzler
Division of Drug Marketing, Advertising and Communications
Food and Drug Administration
HFD-40, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE:

OXYCODONE HYDROCHLORIDE NDA #20-553

Dear Ms. Schnitzler:

Reference is made to our New Drug Application, NDA #20-553 for OxyContin[™] Controlled-Release Tablets, filed December 28, 1994 and approved December 21, 1995. Reference is also made to our promotional launch items filed October 12, 1995 and November 30, 1995; and to a December 20, 1995 letter received by us from the Division of Drug Marketing, Advertising and Promotion (DDMAC) which commented on the submitted launch items.

In accordance with the December 20, 1995 letter from DDMAC, this submission hereby responds to the letter by providing complete responses to each of the comments. A copy of the December 20, 1995 letter immediately follows this letter to facilitate the Division's review of our submission.

Please note that the format of this submission identifies the Division's comment in bold print, and our response in unbolded print. The following revised launch materials are also included herein:

- Visual Aid (version A4847) provided as both a highlighted copy (changes highlighted) and as a clean copy.
- Journal Ad (version A4895)
- Wholesaler Sell Sheet (version A4916-WSS)
- Pharmacy Sell Sheet (version A4916-RSS)
- Titration Guidelines Card (version A4898)
- Conversion Calculator (version A4894)

DEDICATED TO PHYSICIAN AND PATIENT

1/11/96 2

File Card (version A4893)

If you have any questions or require additional information, please contact me at the number given below.

Sincerely yours,

Purdue Pharma L.P.

By:

Lee Ann Storey, RN, MPH

Assistant Director

Drug Regulatory Affairs and Compliance

The Purdue Frederick Company

(203) 854-7285

LAS/cby Enclosures Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 4 of 110. PageID #: 400478

Purdue Pharma L.P.

100 CONNECTICUT AVENUE, NORWALK, CONNECTICUT 06850-3590 + (203) 853-0123 FAX (203) 838-1576

January 11, 1996

RESPONSE TO PROMOTIONAL QUESTIONS

TWO COPIES SUBMITTED
UNDER SEPARATE COVER
TO DIVISION OF DRUG
MARKETING, ADVERTISING
AND COMMUNICATIONS

Robert Bedford, M.D.
Anesthetic/Critical Care & Abuse Drugs
Office of Drug Evaluation 3
Food and Drug Administration
HFD-1330, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 02857

RE:

OXYCODONE HYDROCHLORIDE NDA #20-553

Dear Dr. Bedford:

Reference is made to our New Drug Application, NDA #20-553 for OxyContin[™] Controlled-Release Tablets, filed December 28, 1994 and approved December 21, 1995. Reference is also made to our promotional launch items filed October 12, 1995 and November 30, 1995; and to a December 20, 1995 letter received by us from the Division of Drug Marketing, Advertising and Promotion (DDMAC) which commented on the submitted launch items.

In accordance with the December 20, 1995 letter from DDMAC, this submission hereby responds to the letter by providing complete responses to each of the comments. A copy of the December 20, 1995 letter immediately follows this letter to facilitate the Division's review of our submission.

Please note that the format of this submission identifies the Division's comment in bold print, and our response in unbolded print. The following revised launch materials are also included herein:

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- Pharmacy Sell Sheet (version A4916-RSS)

DEDICATED TO PHYSICIAN AND PATIENT

OxyContin® (oxycodone hydrochloride Controlled-Release) Tablets Response to 12/20/95 DDMAC Letter Anesthetic/Critical Care & Abuse Drugs 1/11/96 2

- Titration Guidelines Card (version A4898)
- Conversion Calculator (version A4894)
- File Card (version A4893)

If you have any questions or require additional information, please contact me at the number given below.

Sincerely yours,

Purdue Pharma L.P.

By:

Lee Ann Storey, RN, MPH

Assistant Director

Drug Regulatory Affairs and Compliance

The Purdue Frederick Company

(203) 854-7285

LAS/cby Enclosures

Food and Drug Administration Rockville MD 20857

DEC 2 0 1995

TRANSMITTED VIA FACSIMILE

James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs and Compliance
The Purdue Frederick Company
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

RE: NDA#20-553

OxyContin (Oxycodone hydrochloride)
MACMIS ID #3673

Dear Dr. Conover:

This is in response to The Purdue Frederick Company's (PF) October 12, 1995, and November 30, 1995, requests for comments on proposed launch materials for OxyContin. These materials include:

OxyContin Launch Visual Aid (version A4847)
OxyContin Journal Ad (version A4895)
OxyContin Wholesaler Sell Sheet (version A4916-WSS)
OxyContin Pharmacy Sell Sheet (version A4916-RSS)
OxyContin Titration Guidelines Card (version A4898)
OxyContin Conversion Calculator (version A4894)
OxyContin File Card (version A4893)

The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and offers the comments that follow. Since many materials contain similar promotional concepts, DDMAC's comments on a specific claim or presentation should be applied to all similar claims or presentations throughout all current and future promotional materials.

Visual Aid A4847

 DDMAC suggests that the footnote information throughout this piece be enlarged because the font size is difficult to read and appears very light in some places.

Page 3

 Prompt onset of relief - analgesic action within 1 hour in most patients

This statement would be misleading because onset of action

page 2

within one hour is not considered prompt relief. In fact, this is a much slower onset than the immediate release formulation, which has an onset of action within fifteen minutes. Additionally, analgesic action within an hour implies that full analgesia occurs within an hour, instead of analgesic onset of action within an hour. DDMAC suggests, for example, "Prompt onset of relief" be deleted and the remaining statement be revised to "analgesic onset within 1 hour in most patients."

4.

-

Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in high daily doses

This statement would be misleading because "high daily doses" is ambiguous and overstates the toxicity. We suggest this be revised, for example, to "...which may be potentially toxic in maximal daily doses."

Common opioid side effects - often diminishing over time for many patients.

DDMAC suggests "except for constipation" be added to this statement because this side effect does not diminish over time.

*

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids is overdosage causing respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

The balancing information should be enlarged because it is not presented with a prominence and readability reasonably comparable to the presentation of information about drug effectiveness.

Additionally, the sentence "The most serious risk associated with opioids is overdosage causing respiratory depression" would be misleading because it implies that respiratory depression only occurs with overdosage. DDMAC suggests this be revised, as consistent with the labeling, such as "The most serious risk associated with opioids, including OxyContin, is respiratory depression."

page 3

Page 4

 The logical next step for patients no longer responding to or tolerating nonopioids: Add to or replace nonopioid with OxyContin.

Q 12 OxyContin - ideal for initial opioid therapy.

OxyContin - The one to start with (Headline - all pages).

These statements would be misleading because they imply that patients not responding to nonopioids should move directly to round-the-clock opiates as the next step in treatment. In fact, prn opioids for mild-to-moderate pain are usually added to the nonopioid therapy as the next step. OxyContin should not be presented as step 2 therapy (mild to moderate pain) on the analgesic pain ladder, because round-the-clock opioids are step 3 therapy (moderate to severe pain). Thus, DDMAC suggests these statements be revised such as "The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids..., ideal for round-the-clock therapy, and the one to start with for round-the-clock therapy."

 Patients are spared the added potential toxicities of high daily doses of ASA or APAP

See comment on under page three regarding maximal doses.

Page 5

 Fewer 'peaks and valleys' than with immediate release oxycodone

This claims OxyContin provides a smoother plasma concentration but fails to include the oxycodone immediate release plasma concentration in the accompanying graph. If PF wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim.

See previous comment on "The one to start with."

Page 6

 Prompt onset of relief: Analgesic action within 1 hour in most patients.

-

page 4

See previous comments.

Percent of patients experiencing onset of pain relief 90%.

This presentation would be misleading because, by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population. Thus, DDMAC recommends that if PF chooses to use this study to support the time to onset, that the introduction be qualified by prominently including the statement from the approved product labeling, "OxyContin is not recommended ... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).

Additionally, this presentation alone would be misleading because it implies pain relief in 90% of patients. However, the studies for approval (402 A and 402 B) showed that 75% of chronic pain patients rated their pain control as good or excellent. Thus, we recommend this presentation also be revised to qualify that the 90% does not correlate to effective pain control.

 Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine

As discussed above, DDMAC would consider "prompt pain relief" to be misleading.

Page 7

Headline - The one to start with.

See previous comment.

Quality of Life Claims

DDMAC cannot comment on these claims until PF submits the following information as requested by telephone on December 1, 1995:

- survey validation,
- survey construction,
- statistical analysis of the results, and
- 4. clinical study and methodology information

PURCHI-000622993

page 5

Page 8

7

 Improved Contin delivery system allows both rapid and prolonged absorption

As discussed above concerning "prompt," DDMAC would consider "rapid" to be misleading and suggests the actual time be stated. For example, "initial release (within an hour)" — would more accurately describe the delivery system.

Rapid Absorption/Prolonged Absorption

See previous comments regarding "prompt" or "rapid."
Additionally, the delivery system does not change the
absorption, it changes the way the drug is released.
Therefore, DDMAC suggests that "rapid absorption" be revised
to "initial release within an hour" and prolonged absorption
to "prolonged release" or "prolonged delivery" to more
accurately describe the biphasic delivery system.

See previous comments regarding "pain relief begins promptly," and "...Oxycodone is rapidly released and absorbed quickly."

Page 9

 DDMAC suggests that PF include balancing information about the risk of overdose if the tablets are broken with the delivery system presentation.

Page 12

Steady state blood levels achieved in 24 hours.

This should be revised to "steady state blood levels achieved in 24 to 36 hours," as consistent with the approved labeling.

Page 14

 Most side effects diminished over time, even as daily doses increased.

DDMAC suggests that this presentation include a statement that the most serious risk associated with opioids is respiratory depression.

page 6

Page 16 and 17

-

These pages present dosing and titration information but fail to include information from the warnings section of the approved labeling about high risk persons who may need a decrease in dosage. DDMAC suggests information be added to this presentation such as "respiratory depression is the most serious unintended effect of all opioid agonist preparations. Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See Warnings and precautions."

Back Page

Small, color-coded tablets are easy to identify and swallow
 an important benefit for patients on multiple medications

DDMAC questions whether the color-coded tablets are easy to identify for patients who are taking multiple medications that include other small, white, pink or yellow tablets.

This summary page contains several statements which DDMAC has commented on in this letter. The back page should be consistent with the revisions made throughout the visual aid.

Journal Ad

Comments on the claims in the visual aid should be applied to the journal ad.

Wholesaler Sheet

Warning-May be habit forming

DDMAC suggests this statement be enlarged to increase its prominence because the typesize is difficult to read.

Strong demand expected

DDMAC has received the materials from the intent to prescribe survey. However, we cannot evaluate the data unless more information is provided about the methodology. Such a description should include how participants were selected, the refusal rate, the geographic distribution and other demographic data, and how the questionnaire was administered. For example, was it presented by the sales representative immediately after a presentation or was it

page 7

done in groups?

Balance information (back page).

See DDMAC's comments on the visual aid.

Pharmacy Sell Sheet

See comments on wholesaler sheet.

Titration Guidelines Card, Conversion Calculator, and File Card

See DDMAC's comments under visual aid.

If Purdue Frederick has any questions or comments, please contact the undersigned by facsimile (301) 594-6771 or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, 5600 Fishers Lane, HFD-40, Room 17B-20, Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to MACMIS ID #3673, in addition to the NDA number.

Sincerely,

Diane Shnitzler

Regulatory Review Officer Division of Drug Marketing,

Advertising and Communications

PURCHI-000622996

1/11/96

1

RESPONSE TO COMMENTS

Visual Aid A4847

 DDMAC suggests that the footnote information throughout this piece be enlarged because the font size is difficult to read and appears very light in some places.

Reply:

The footnote information throughout the piece has been enlarged.

Page 3

prompt onset of relief - analgesic action within 1 hour in most patients

This statement would be misleading because onset of action within one hour is not considered prompt relief. In fact, this is a much slower onset than the immediate release formulation, which has an onset of action within fifteen minutes. Additionally, analgesic action within an hour implies that full analgesia occurs within an hour, instead of analgesic <u>onset</u> of action within an hour. DDMAC suggests, for example, "Prompt onset of relief" be deleted and the remaining statement be revised to "analgesic onset within 1 hour in most patients."

Reply:

The statement

"Prompt onset of relief - analgesic action within 1 hour in most patients"

was revised to read.

"Analgesic onset within 1 hour - in most patients"

The above question states that the immediate-release formulation has an onset of action within fifteen minutes. Our data for the immediate-release formulation of oxycodone shows the onset of action is within 41 minutes. Please refer us to the studies which demonstrate a fifteen minute onset with immediate-release oxycodone, as we have not been able to find this in the literature.

1/11/96

2

 Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in high daily doses

This statement would be misleading because "high daily doses" is ambiguous and overstates the toxicity. We suggest this be revised, for example, to "...which may be potentially toxic in maximal daily doses."

Reply:

The statement,

"Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in high daily doses"

was revised to read,

"Single-entity agent - contains no aspirin or acetaminophen which may be potentially toxic in maximal daily doses"

Common opioid side effects - often diminishing over time for many patients.

DDMAC suggests "except for constipation" be added to this statement because this side effect does not diminish over time.

Reply:

The statement,

"Common opioid side effects - often diminshing over time for many patients."

was revised to read,

"Common opioid side effects - often diminishing over time for many patients, except for constipation."

 OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose

1/11/96

3

of oxycodone. The most serious risk associated with opioids is overdosage causing respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating

The balancing information should be enlarged because it is not presented with a prominence and readability reasonably comparable to the presentation of information about drug effectiveness.

Additionally, the sentence "The most serious risk associated with opioids is overdosage causing respiratory depression" would be misleading because it implies that respiratory depression only occurs with overdosage. DDMAC suggests this be revised, as consistent with the labeling, such as "The most serious risk associated with opioids, including OxyContin, is respiratory depression."

Reply:

Visual aid revised accordingly

and weakness.

Page 4

- a) The logical next step for patients no longer responding to or tolerating nonopioids: Add to or replace nonopioid with OxyContin.
 - b) Q 12 OxyContin ideal for initial opioid therapy.
 - c) OxyContin The one to start with (Headline all pages).

These statements would be misleading because they imply that patients not responding to nonopioids should move directly to round-the-clock opiates as the next step in treatment. In fact, prn opioids for mild-to-moderate pain are usually added to the nonopioid therapy as the next step. OxyContin should not be presented as step 2 therapy (mild to moderate pain) on the analgesic pain ladder, because round-the-clock opioids are step 3 therapy (moderate to severe pain). Thus, DDMAC suggests these statements be revised such as "The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids..., ideal for round-the-clock therapy, and the one to start with for round-the-clock therapy."

PURCHI-000622999

1/11/96

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Reply:

a) The statement,

"The logical next step for patients no longer responding to or tolerating nonopioids" was replaced with,

"The logical next step for patients with persistent pain, no longer responding to or tolerating nonopioids"

The revision differs slightly from the suggested revision ("The logical next step for patients no longer responding to or tolerating nonopioids and prn opioids...), because we disagree with the FDA interpretation of the WHO analgesic ladder¹. Step 2 does not address dosing analgesics on a prn basis. Step 2 relates to adding an opioid to the therapeutic regimen in patients who have persisting pain in the presence of a non-opioid analgesic ± an analgesic adjuvant. While we recognize that common medical practice is to treat with non-opioids, then add or change to prn opioids or opioid/non-opioid combination products, and then advance to around-the-clock (a-t-c), this approach is not the best medical practice. This approach can lead to underdosing and episodes of breakthrough pain. Various publications and consensus statements support the use of a-t-c, not prn, medications for persistent pain syndromes. For example,

"Administer analgesics regularly (not prn) if pain is present most of the day"2

"Medications for persistent cancer-related pain should be administered on an around-the-clock basis with additional "as-needed" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain."

"Medication should be administered on a regular basis with the interval between doses based on the duration of the analgesic effect."

While we recognize common medical practice, our goal, as a responsible company, is to foster education in the proper use of analgesics. In this way patients will be more likely to have continuing adequate pain control and relief.

1/11/96

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¹ Cancer Pain Relief. World Health Organization. Geneva. 1986. p. 19

Management of Cancer Pain. AHCPR Clinical Practice Guideline Number 9, March 1994, p. 39.

⁴ Foley KM. The Treatment of Cancer Pain. New Eng J Med 313 (2): 84-95, 1985

b) The statement,

"Q 12 OxyContin - ideal for initial opioid therapy"

was revised to read.

"Q 12 OxyContin - ideal for initial around-the-clock (A-T-C) opioid therapy"

c) The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read.

"OxyContin - The one to start with (A-T-C)"

footnote and prior caption defines "A-T-C" as around the clock

 Patients are spared the added potential toxicities of high daily doses of ASA or APAP

See comment on under page three regarding maximal doses.

Reply:

The statement,

"Patients are spared the added potential toxicities of high daily doses of ASA or APAP" was revised to read,

² Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. American Pain Society. 3rd edition 1992. p. 16

1/11/96

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"Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP"

Page 5

Fewer 'peaks and valleys' than with immediate release oxycodone

This claims OxyContin provides a smoother plasma concentration but fails to include the oxycodone immediate release plasma concentration in the accompanying graph. If PF wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim.

Reply:

The comparative statement, "Fewer peaks and valleys' than with immediate-release oxycodone" was deleted.

See previous comment on "The one to start with."

The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read.

"OxyContin - The one to start with (A-T-C)"

footnote and prior caption defines "A-T-C" as around the clock

Page 6

Prompt onset of relief: Analgesic action within 1 hour in most patients.

See previous comments.

1/11/96

7

Reply:

The statement, "Prompt onset of relief" was deleted.

The statement,

"Analgesic action within 1 hour in most patients"

was revised to read.

"Analgesic onset within 1 hour in most patients"

Percent of patients experiencing onset of pain relief 90%.

This presentation would be misleading because, by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population. Thus, DDMAC recommends that if PF chooses to use this study to support the time to onset, that the introduction be qualified by prominently including the statement from the approved product labeling, "OxyContin is not recommended... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).

Additionally, this presentation alone would be misleading because it implies pain relief in 90% of patients. However, the studies for approval (402A and 402B) showed that 75% of chronic pain patients rated their pain control as good or excellent. Thus, we recommend this presentation also be revised to qualify that the 90% does not correlate to effective pain control.

Reply:

Reference to postoperative patients was deleted from the footnote (i.e., "From a single-dose study in postoperative patients" was revised to, "From a single-dose study"). Because this reference to postoperative patients was deleted we do not believe it is necessary to include the suggested statement ["OxyContin is not recommended... for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery")]

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8

The statement relating to 90% pertains to analgesic "onset", not pain relief. We have revised the statement to further clarify this (i.e., "Percent of patients experiencing onset of pain relief" was revised to, "Percent of patients experiencing analgesic onset")

 Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine

As discussed above, DDMAC would consider "prompt pain relief" to be misleading.

Reply:

The statement,

"Prompt pain relief plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine"

was revised to read.

"Analgesic onset within one hour plus a longer duration of action than Percocet, Vicodin, or Tylenol with Codeine"

Page 7

Headline - The one to start with.

See previous comment.

Reply:

The statement,

"OxyContin - The one to start with (Headline - all pages)"

was revised to read.

"OxyContin - The one to start with (A-T-C)"

footnote and prior caption defines "A-T-C" as around the clock

1/11/96

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Quality of Life Claims

DDMAC cannot comment on claims until PF submits the following information as requested by telephone on December 1, 1995:

- 1. survey validation,
- 2. survey construction,
- 3. statistical analysis of the results, and
- 4. clinical study and methodology information

Reply:

The above information was submitted to DDMAC on December 19, 1995.

The statement (as proposed prior to finalization of the Package Insert),

"Patients reported that OxyContin did not impair their ability to;

Sleep

- Perform Normal Work
- · Get along with other people

Walk

Enjoy Life

was revised, in accordance with the approved Package Insert, Section: CIINICAL TRIALS, Subsection: Studies in Non-Cancer Pain, to

- "- In this study, OxyContin 20 mg q12h...
 - Significantly decreased pain
 - Improved quality of life, mood and sleep"

We believe the Package Insert most accurately describes the results of this study.

Page 8

Improved Contin delivery system allows both rapid and prolonged absorption

As discussed above concerning "prompt," DDMAC would consider "rapid" to be misleading and suggests the actual time be stated. For example, "initial release (within an hour)" would more accurately describe the delivery system.

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Reply:

The statement,

"Improved Contin® delivery system allows both rapid and prolonged absorption."

was revised to read.

"Improved Contin® delivery system allows both rapid and prolonged release."

Rapid absorption/Prolonged Absorption

See previous comments regarding "prompt" or "rapid." Additionally, the delivery system does not change the absorption, it changes the way the drug is released. Therefore, DDMAC suggests that "rapid absorption" be revised to "initial release within an hour" and prolonged absorption to "prolonged release" or "prolonged delivery" to more accurately describe the biphasic delivery system.

See previous comments regarding "pain relief begins promptly," and "...Oxycodone is rapidly released and absorbed quickly."

Reply:

a) The statement,

Rapid absorption Pain relief begins promptly as a portion of the active oxycodone is rapidly released and absorbed quickly."

was revised to read,

Rapid release Analgesic onset within one hour as a portion of the active oxycodone is released and absorbed."

b) The statement,

"Prolonged absorption"

was revised to read,

"Prolonged release"

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In addition, the layout of the illustration text was changed so as not to give the inadvertent impression that the rapid release occurs only in the stomach, and prolonged release occurs only in the intestine. Release of drug is not dependent upon its location in the gastrointestinal tract (i.e., no pH dependence).

To further define the tablet release characteristics, the statement "pH independence" assures...Minimal effect of stomach contents on absorption-bioavailability unaffected by food" was moved from the bottom of page 9 to the bottom of page 8.

Page 9

 DDMAC suggests that PF include balancing information about the risk of overdose if the tablets are broken with the delivery system presentation.

Reply:

This balancing information was added to the bottom of page 9.

Page 12

Steady state blood levels achieved in 24 hours.

This should be revised to "steady state blood levels achieved in 24 to 36 hours," as consistent with the approved labeling.

Reply:

The statement,

"Steady state blood levels achieved in 24 hours"

was revised to read,

"Steady -State blood levels achieved in 24-36 hours

PURCHI-000623007

1/11/96

12

Page 14

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Most side effects diminished over time, even as daily doses increased.

DDMAC suggests that this presentation include a statement that the most serious risk associated with opioids is respiratory depression.

Reply:

The statement. a)

"Common opioid side effects; many diminish over time."

was revised to read,

"Common opioid side effects; many diminish over time except for constipation."

- the following statement was added as a bullet point under the side effect Table, b)
 - "- The most serious risk associated with opioids is respiratory depression."
- C) The statement,
 - "-Most side effects diminished over time, even as daily doses increased" was revised to read,
 - "Most side effects diminished over time, except for constipation, even as daily doses increased"

Page 16 and 17

These pages present dosing and titration information but fail to include information from the warnings section of the approved labeling about high risk persons who may need a decrease in dosage. DDMAC suggests information be added to this presentation such as "respiratory depression is the most serious unintended effect of all opioid agonist preparations. Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant

1/11/96

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patients, or when opioids are given in conjunction with other agents that depress respiration. See Warnings and Precautions."

Reply:

The following statement was added,

"Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS."

The proposed initial sentence, "respiratory depression is the most serious unintended effect of all opioid agonist preparations." was not added because we believe respiratory depression is addressed sufficiently in the remainder of the statement as well as on pages 3 and 14 of this visual aid.

Back Page

 Small, color-coded tablets are easy to identify and swallow - an important benefit for patients on multiple medications

DDMAC questions whether the color-coded tablets are easy to identify for patients who are taking multiple medications that include other small, white, pink or yellow tablets.

Reply:

The statement,

"-Small, color-coded tablets are easy to identify and swallow- an important benefit for patients on multiple medications"

was revised to read,

"- Small, color-coded tablets are easy to identify and swallow"

This summary page contains several statements which DDMAC has commented on in this letter. The back page should be consistent with the revisions made throughout the visual aid.

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14

Reply:

The back page has been revised to be consistent with the revisions made throughout the visual aid.

In addition to the above changes, pages 16 and 17 were revised to delete the statements pertaining to "q3-4h prn" and to add the statement "* See professional prescribing information for immediate-release oxycodone."

Throughout the visual aid the statement, "Please see accompanying full prescribing information." was revised to read, "Please see accompanying professional prescribing information."

Journal Ad

Comments on the claims in the visual aid should be applied to the journal ad.

Reply:

Revised in accordance with the visual aid.

Wholesaler Sheet

Warning-May be habit forming

DDMAC suggests this statement be enlarged to increase its prominence because the type size is difficult to read.

Reply:

Revised in accordance with the visual aid.

Strong demand expected

DDMAC has received the materials from the intent to prescribe survey. However, we cannot evaluate the data unless more information is provided about the methodology. Such a description should include how participants were selected, the refusal rate, the geographic distribution and other

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demographic data, and how the questionnaire was administered. For example, was it presented by the sales representative immediately after a presentation or was it done in groups?

Balance information (back page).

See DDMAC's comments on the visual aid.

Reply:

In order to expedite distribution of the Wholesaler sheet, we deleted all promotional statements from this sheet. Therefore statements based on the intent to prescribe survey were also deleted.

Attached is a copy of the redesigned Wholesaler Sheet.

Pharmacy Sell Sheet

See Comments on wholesaler sheet.

Reply:

In order to expedite distribution of the Pharmacy Sell sheet, we deleted any promotional statements from this sheet.

Attached is a copy of the redesigned Pharmacy Sell Sheet.

Titration Guidelines Card, Conversion Calculator, and File Card

See DDMAC's comments under visual aid.

Reply:

Revised in accordance with the visual aid.

The Conversion Calculator (refer to highlighted version) has been revised to:

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- round down the recommended conversion doses to allow for use of one tablet strength.
 This cautionary change was made to prevent possible administration errors if patients should be directed to take two tablet strengths as the prescribed dose. The conversion doses remain consistent with Table 4 in the DOSAGE AND ADMINISTRATION Section of the Package Insert.
- alter the recommended conversion dose of OxyContin tablets when patients are converted from controlled-release oral morphine(MS Contin[®]). These doses were altered to better coordinate with MS Contin[®] dosage strengths.

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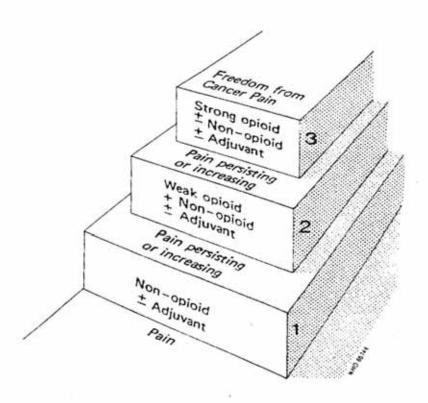
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World Health Organization, Geneva



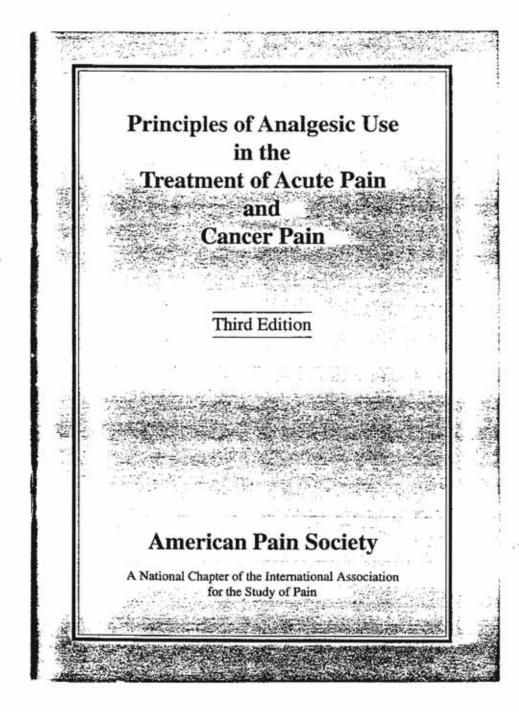
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Adjuvant drugs are often needed in patients with pain secondary to nerve injury. There is evidence to suggest that they provide additive analgesic effects (49) and controlled studies demonstrate the analgesic efficacy of, for example, amitriptyline (16). Corticosteroids are commonly used in patients with cancer both as chemotherapeutic agents and as analgesics. Several studies have reported relief of pain by corticosteroids in patients with epidural spinal cord compression or infiltration of a nerve by the tumour, and also in metastatic bone disease (50, 51). Useful adjuvant drugs are listed in Annex 1, Table 3.

On the basis of considerable clinical experience and of controlled studies of analgesics, a series of important principles have been established:



venous patient-controlled analgesia following cesarean section, mean demand rates varied from 0.6 to 5.2 mg per hour. This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain. Elderly patients and patients with central nervous system disease should be observed with particular care during dose titration to minimize adverse reactions. Intramuscular morphine produces a longer duration of analgesia in older patients, in part related to prolonged elimination from plasma (Kaiko et al., 1986). For patients over 70, one should consider lowering the starting doses in Table 3 by 25% to 50%.

c. Give each analgesic an adequate trial by dose titration (i.e., increasing the dose up to the appearance of limiting side effects) before switching to another drug.

Administer analgesics regularly (not prn) if pain is present most of the day.

This should be done after establishing the optimal dose by titration—that is, giving a typical starting dose and increasing or decreasing the dose according to the degree of pain relief and side effects experienced by the patient. Once the optimal dose requirements for a 24-hour period have been established by titration, the analgesics can be administered on a scheduled, around-the-clock basis with fewer side effects. A pm order for a supplementary opioid dose between regular doses is an essential backup. If only pm medications are used, it may take several hours and higher doses of opioids to relieve pain, leading to a cycle of undermedication and pain alternating with periods of overmedication and drug toxicity. It is particularly important that children and patients with limited communication skills do not receive a pm-only regimen. If pain is present for only a few brief periods during the day, the patient can regularly be offered a standard analgesic dose, or the choice of a larger or smaller dose.

3. Become familiar with the dose and time-course of several strong opioids.

While morphine is the standard strong opioid, all morphine-like agonists (see Table 3, a) provide similar qualities of analgesia and similar qualities and frequency of side effects. In practice, however, individual

Clinical Practice Guidelin Clinical Practice Guideline Management of Cancer Pain Management of Cancer Pain U.SIDepartment of Health and Human Service PublicHealth Services Agency for Health Care Policy and Research

3 Pharmacologic Management

Recommendations

- 13. An essential principle in using medications to manage cancer pain is to individualize the regimen to the patient. (A)
- The simplest dosage schedules and least invasive pain management modalities should be used first. (Panel Consensus)
- Pharmacologic management of mild to moderate cancer pain should include an NSAID or acetaminophen, unless there is a contraindication. (A)
- 16. When pain persists or increases, an opioid should be added. (A)
- Treatment of persistent or moderate to severe pain should be based on increasing the opioid potency or dose. (A)
- 18. Medications for persistent cancer-related pain should be administered on an around-the-clock basis with additional "asneeded" doses, because regularly scheduled dosing maintains a constant level of drug in the body and helps to prevent a recurrence of pain. (A)
- Patients receiving opioid agonists should not be given a mixed agonist-antagonist because doing so may precipitate a withdrawal syndrome and increase pain. (B)
- Meperidine should not be used if continued opioid use is anticipated. (B)
- Opioid tolerance and physical dependence are expected with longterm opioid treatment and should not be confused with addiction. (Panel Consensus)
- 22. The oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective method of administration. When patients cannot take medications orally, rectal and transdermal routes should be considered because they are also relatively noninvasive. (Panel Consensus)
- Intramuscular administration of drugs should be avoided because this route can be painful and inconvenient, and absorption is not reliable. (B)
- Failure of maximal systemic doses of opioids and coanalgesics should precede the consideration of intraspinal analgesic systems. (Panei Consensus)

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MEDICAL PROGRESS

THE TREATMENT OF CANCER PAIN

KATHLEEN M. FOLEY. M.D.

ADVANCES in the diagnosis and treatment of cancer, coupled with an expanded understanding of the physiology, pharmacology, and psychology of pain perception, have led to improved care of the patient with pain from cancer. Improved methods of cancer diagnosis and treatment provide the best approach to managing pain by treating its cause. Before the start of antitumor therapy or when such therapy is unsuccessful or irreversible injury to bone, soft tissue, or nerve has occurred, however, adequate pain control is essential.

Management of pain in patients with cancer requires specific expertise that includes a knowledge of the clinical pain syndromes that are common in cancer and their pathophysiologic mechanisms, the psychological state of the patient, and the indications and limitations of the available therapeutic approaches. Clinical experience suggests that patients with cancer pain are treated most effectively with a multidisciplinary approach that includes adequate analgesic drug

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therapy, neurosurgical and anesthetic procedures, behavioral methods, and supportive care. 2-5

The goal of pain therapy for patients receiving active treatment is to provide them with sufficient relief to tolerate the diagnostic and therapeutic approaches required to treat the cancer. For patients with advanced disease, pain control should be sufficient to allow the patients to function at a level that they choose and to die relatively free of pain. ^{6,7} Critical to the management of cancer pain is the establishment of a trusting relationship between the patient and a physician who takes the pain seriously and assesses its nature and severity.

EPIDEMIOLOGY

Large-scale epidemiologic studies of the incidence and severity of cancer pain are lacking, but numerous studies in specialized medical care settings have demonstrated that the prevalence of pain increases with the progression of disease. Patients with cancer frequently have multiple causes of pain. Some 15 per cent of patients with nonmetastatic cancer have pain. One third of adults and children with metastatic cancer report pain that interferes with and reduces their activity level and requires the use of analgesics. With advanced disease, 60 to 90 per cent of patients report

substantial pain. 3.11.12 It is postulated that 25 per cent of all patients with cancer throughout the world die without relief from severe pain. To remedy this situation and as part of a broader cancer program, the Cancer Unit of the World Health Organization has formulated a pain-relief program to conduct an epidemiologic investigation of cancer pain throughout the world, to provide guidelines for pain management, particularly in patients with advanced disease, and to encourage national governments to help make therapeutic approaches available, specifically oral narcotic drug therapy. 13

TYPES OF PAIN

Patients with cancer have two types of pain: acute and chronic. This division is based on an increased understanding of the mechanisms of pain transmission and the recognition that the central modulation of acute and chronic pain states may differ, along with their clinical management and response to treatment. 14.15 For this discussion the definition of pain proposed by the International Association for the Study of Pain is most useful: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." 16 Because pain is a subjective experience, evaluation of it is difficult. The physician has limited objective signs to confirm the severity of reported pain. The patient and physician are best served if the physician believes the patient's report.

Acute pain is characterized by a well-defined temporal pattern of onset. It is generally associated with subjective and objective physical signs and hyperactivity of the autonomic nervous system. These signs serve as objective evidence to the physician, substantiating the patient's report of pain. In contrast, chronic pain is pain that persists longer than six months, in which adaptation of the autonomic nervous system occurs. Patients with chronic pain lack the objective signs common to acute pain. Chronic pain leads to marked changes in personality, life style, and functional ability. Such pain requires an approach that encompasses not only treatment of the cause of the pain but also treatment of its psychological and social consequences. 15,17

Patients with chronic or acute pain from cancer can be further subdivided, providing the physician with a useful classification when considering therapeutic approaches (Table 1).

Group I comprises patients with acute cancer-related pain. A subgroup of this category includes patients in whom pain is the major symptom leading to the diagnosis of cancer. For this group, pain has a special meaning as the harbinger of their illness. The occurrence of pain during the course of the illness or after successful therapy has the immediate implication of recurrent disease. Determination of the cause of the pain may present a diagnostic problem, but effective treatment of the cause — e.g., irradiation of bone me-

Table 1. Types of Patients with Pain from Cancer.

- I. Patients with acute cancer-related pain
 - a. Associated with the diagnosis of cancer
 - b. Associated with cancer therapy (surgery, chemotherapy, or radiation)
- II. Patients with chronic cancer-related pain
 - a. Associated with cancer progression
 - b. Associated with cancer therapy (surgery, chemotherapy, or radiation)
- III. Patients with preexisting chronic pain and cancer-related pain
- IV. Patients with a history of drug addiction and cancer-related pain
- a. Actively involved in illicit drug use
 - in methadone maintenance programs
 - c. With a history of drug abuse
- V. Dying patients with cancer-related pain

tastases — is usually possible and is associated with dramatic pain relief in the majority of patients.

The second subgroup includes patients who have acute pain associated with cancer therapy — e.g., pain after surgery or secondary to the acute effects of chemotherapy. The cause of the pain is readily identified, and its course is predictable and self-limited. Such patients endure pain for the promise of a successful outcome.

Group II, which consists of patients with chronic cancer-related pain, represents difficult diagnostic and therapeutic problems. This group can be subdivided into patients with chronic pain from tumor progression and those with chronic pain related to cancer treatment. Both subgroups have pain that has persisted for more than six months.

In patients with chronic pain associated with the progression of disease — e.g., those with carcinoma of the pancreas — the pain escalates in intensity, and combinations of antitumor therapy, analgesic drug therapy, anesthetic blocks, and behavioral approaches to pain control are all attempted with varying degrees of success.

Psychological factors play an important part in this group of patients, in whom palliative therapy may be of little value and is physically debilitating.11,18 The sense of hopelessness and fear of impending death may add to and exaggerate the pain, which in turn contributes to the overall suffering of the patient. Identification of both the pain and the suffering component is essential to the provision of adequate therapy. Saunders has used the phrase "total pain" to describe the etiologic components other than the noxious physical stimulus, including emotional, social, bureaucratic, financial, and spiritual pain. Those caring for this group of patients must be concerned with all aspects of distress and discomfort if the experience of physical pain is to be alleviated. The chronicity of the pain is associated with a series of psychological signs -e.g., disturbances in sleep, reduction in appetite, impaired concentration, and irritability - and with clinical signs and symptoms mimicking a depressive disorder. 1

Patients with chronic pain associated with cancer therapy usually require treatment directed at the symptoms, not the cause. Treatment of the pain is often limited by the lack of available methods to remove the cause of the pain — e.g., a traumatic neuroma. This group of patients closely parallels those in the general population with chronic, intractable pain. Identification of this group of patients is imperative, because recognition of the cause of the pain as independent of the cancer markedly alters the patient's therapy, prognosis, and psychological state. All approaches intended to maintain the functional status of the patient should be employed. 15.17 Approaches other than drug therapy provide effective alternatives for pain management. This group is increasing in size and accounts for 25 per cent of patients referred to one cancer pain clinic. 10

Group III includes patients with a history of chronic, nonmalignant pain who have cancer and associated pain. Psychological factors play an important part in these patients, whose psychological and functional status is already compromised. They are at high risk of further functional incapacity and escalating chronic pain. However, their history should not be used in a punitive way to minimize their complaints. Identification of this group of patients as a high-risk group helps to improve their psychological assessment and intervention.

Group IV includes patients with a history of drug addiction who have cancer-related pain. Three subgroups can be identified: patients actively involved in illicit drug use and drug-seeking behavior, those receiving methadone in a maintenance program, and those who have not used drugs for several years. Undertreatment with analgesic drugs occurs most commonly in this group of patients. Assessment of reported pain by physicians and nurses is colored by the fact hat the pain symptoms are confused with drug-seeking behavior. Attention to the medical and psychological needs of these patients requires individualized assessment and consultation with experts in drugrelated problems. 18 The first subgroup represents a major management problem, straining the most tolerant of medical care systems. Pain in the other two subgroups is readily managed, with the recognition that the psychological stresses consequent to the pain and cancer may place the patient at high risk for recidivism.

Group V includes dying patients with pain. In this group diagnostic and therapeutic considerations should be directed at maintaining the comfort of the patient. The issues of hopelessness, death, and dying become prominent, and the suffering component of the illness must be addressed. Inadequate control of pain exacerbates the suffering and demoralizes both the family and the medical personnel, who feel that they have failed in treating the patient's pain at a time when adequate treatment may matter most. Rapid escalation of analgesic drug therapy and attempts to ameliorate the psychological symptoms should be employed. The risk-benefit ratios associated with analgesic approaches become less of an issue when the goal of pain therapy is the comfort of the patient.

These types of cancer pain point up the necessity of understanding the psychological needs of the patient and the temporal factors in order to assess the pain and manage it appropriately.

Cancer pain has also been classified according to a series of common pain syndromes and their pathophysiologic mechanisms. ¹² The pain syndromes that commonly occur in patients with cancer have been divided into three major categories.

The first and most common cause of pain in patients with cancer is that associated with direct tumor involvement. This accounted for 78 per cent of pain problems in a survey of the Memorial Sloan-Kettering Cancer Center inpatient population⁵ and for 62 per cent of problems in an outpatient survey.⁹ Metastatic bone disease, nerve compression or infiltration, and hollow viscus involvement are the most common causes of pain from direct tumor involvement.

The second group of pain syndromes are those associated with cancer therapy. This group accounts for approximately 19 per cent of pain problems in an inpatient population and 25 per cent of problems in outpatients. It includes pain that occurs in the course of or as a result of surgery, chemotherapy, or radiation therapy.

The third category of pain syndromes includes those unrelated to the cancer or the cancer therapy. Approximately 3 per cent of inpatients have pain unrelated to cancer or cancer therapy, and this figure increases to 10 per cent when an outpatient population is surveyed.

The pathophysiologic mechanisms of these common pain syndromes are not well understood. It is currently thought that a series of neuropharmacologic and neurophysiologic changes occur in bone, soft tissue, lymphatics, blood vessels, nerve and viscera, activating and sensitizing nociceptors and mechanoreceptors by mechanical (tumor compression or infiltration) or chemical (metastases in bone) stimuli. Acute, intermittent, or continuous pain results. Most therapeutic approaches are partially effective in controlling this kind of pain. 19 In contrast, pain from nerve injury after nerve section or chronic tumor infiltration or compression produces partial damage of axons and nerve membranes, which become extremely sensitive to any mechanical or chemical stimuli. Chronic unremitting pain results, which is poorly controlled by the majority of therapeutic approaches. Experimental studies indicate that pain from deafferentation leads to central neuronal hyperactivity in the spinal cord and, possibly, in the thalamus.20

These different physiologic mechanisms account in part for the differences in the responses of various types of cancer pain to analgesic, neurosurgical, and anesthetic approaches. For example, drug therapy and neurosurgical procedures are often effective in managing pain from lumbosacral plexopathy in its early acute stage, but once deafferentation has occurred, the success of such procedures diminishes rapidly.²⁰

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MANAGEMENT OF CANCER PAIN

There are certain general principles that should be followed in evaluating all patients with cancer and pain.21 Lack of attention to these principles is the major cause of misdiagnosis and inappropriate management of a specific pain syndrome. The principles include a complete assessment of the history of pain and an evaluation of the psychosocial status of the patient. A careful medical and neurologic examination must be coupled with the use of appropriate diagnostic procedures to determine the nature of the pain. Early treatment with analgesics markedly improves the patient's ability to participate in these procedures. No patient should be inadequately evaluated because of pain. Continual reassessment of the patient's response to prescribed therapy provides the best method of validating the accuracy of the initial diagnosis. If the response to therapy is less than predicted or if exacerbation of pain occurs, reassessment of the treatment approach or a search for a new cause of pain should be considered. Management of pain in patients with cancer requires continuity of care from the diagnosis to treatment.22

THERAPEUTIC APPROACHES

Non-narcotic, narcotic, and adjuvant analgesic drugs are the mainstay of therapy for patients with cancer pain. Effective use of these drugs requires an understanding of their clinicopharmacologic characteristics, with selection of a particular drug and dose geared to the needs of the individual patient. Neurosurgical, anesthetic, and behavioral approaches are commonly used in combination with drug therapy.

Changing attitudes toward the use of narcotic analgesics for cancer pain coupled with the recognition of the dynamic complexity of pain modulation have led to reassessment of the role of anesthetic and neurosurgical approaches. These approaches are most useful for managing localized pain before the development

of serious nerve injury and a consequent deafferentation state. Although these procedures have been widely used, controlled studies of their effectiveness, as compared with that of other methods of pain control, are lacking. Published reports provide survey data on techniques and successful outcome in small numbers of patients.

These techniques require specific expertise, and certain guidelines apply to their use. These include a thorough evaluation of the nature of the pain and the patient's prognosis, an adequate prior trial of analgesic drug therapy and anticancer therapy, and the patient's awareness of the potential risks and benefits of the planned procedures. The

types of anesthetic and neurosurgical procedures are listed in Tables 2 and 3. Historically, these procedures have been employed late in the course of a patient's illness, and full assessment of their efficacy has been limited by disease progression and diffuse as well as focal pain. Many patients prefer to defer these procedures until they complete their anticancer therapy, with the hope that such therapy will provide relief. Also, when informed about the small but potential risk of neurologic impairment associated with these procedures, many patients are not willing to accept such a risk for pain control alone.

There is a need to develop strategies for the appropriate use of these procedures. A detailed review of them is beyond the scope of this discussion. Drug therapy is stressed in the following discussion, because all physicians caring for patients with pain must develop competence and confidence in the use of drugs.

Drug Therapy

Non-narcotic Agents

Non-narcotic analgesics are the first-line agents for the management of mild to moderate cancer pain. 22-25 In patients with severe pain these drugs serve to potentiate the effects of narcotic analgesics. Non-narcotic analgesics have a ceiling effect, and their long-term use is limited by gastrointestinal and hematologic side effects. In contrast to narcotic analgesics, non-narcotic agents do not cause tolerance or physical dependence.

There is increasing evidence to suggest that these drugs may have a unique role in the management of certain kinds of pain from bone metastases. 26-28 Anecdotal reports indicate that both aspirin and indomethacin relieve bone pain, and in an animal tumor model, aspirin has been shown to have antitumor effects. These effects are thought to be mediated in part through inhibition of prostaglandin synthesis, specifically prostaglandin E2, which is important in the development of bone metastases in solid tumors.

Table 2. Neuroablative, Neurostimulatory, and Neuropharmacologic Procedures for Relief of Pain from Cancer.

SITE	PROCEDURE				
	NEUROABLATIVE	MEUROSTIMULATORY	PHARMACOLOGIC		
Peripheral nerve	Neurectomy	Transcutaneous and per- cutaneous electrical nerve stimulation	Local anesthetics		
Nerve root	Rhizotomy		Local anesthetics Neurolytic agents		
Spinaž cord	Dorsal-root entry- zone lesions Cordotomy Myelotomy	Dorsal-column stimulation	Epidural and intra- thecal local anes- thetics and opiates		
Brain stem	Mesencephatic tractotomy	Periaqueductal stimulation	Intraventricular opiates		
Thalamus	Thalamotomy	Thalamic stimulation			
Cortex	Cingulumotomy Frontal lobotomy	•A			
Pituitary	Transsphenoidal hypoph- ysectomy		Chemical hypoph- ysectomy		

Table 3. Types of Anestnetic Procedures Commonly Used for Cancer Pain.

Type or Procedure	MOST COMMON INDICATIONS		
Nerve block			
Peripheral	Pain in discrete dermatomes in chest and abdomen		
Epidural	Unilateral lumbar or sacral pain		
	Midline perincal pain		
	Silateral lumbosacral pain		
intruthecal	Midline permeal pain		
	Bilateral lumbosacral pain		
Autonomic			
Stellate ganglion	Reflex sympathetic dystrophy (e.g., frozen shoulder)		
	Arm pain		
Lumbar sympathetic	Reflex sympathetic dystropny		
Little on Perueboniocon	Lumbosacral plexopathy		
	Vascular insufficiency of the lower extremity		
Cetiac plexus	Midabdominal pain		
Continuous epidural infusion	Unilateral and bilateral lumposacral pair		
with local anesthetics	Midline perineal pain		
Chemical hypophysectomy	Diffuse bone pain		
Inhalation therapy	Generalized pain Incident pain		
Trigger-point injection	Focal muscle pain		

The choice and use of these drugs must be individualized, with the patient receiving maximal levels of one drug before another is tried. Combinations of nonsteroidal and antiinflammatory drugs that produce additive analgesia remain controversial. If pain control is ineffective or the non-narcotic agents are poorly tolerated, the use of narcotic analgesics is indicated.

Narcotic Analgesics 🐇

The narcotic analgesics are classified as agonist or antagonist drugs, depending on their ability to bind to opiate receptors and produce analgesia. The narcotic agonist drugs, such as morphine, bind to specific opiate receptors, resulting in analgesia. These drugs are commonly used in the management of cancer pain. The narcotic antagonist drugs block the effect of morphine at its receptor. Included in this category is a group of drugs with analgesic properties referred to as "mixed agonist-antagonist" drugs.29 These drugs are of limited use in patients with cancer for several reasons: they produce psychotomimetic effects with increasing doses; except for pentazocine, they are available only for parenteral administration (nalbuphine and butorphanol); oral pentazocine is available only in combination with naloxone, aspirin, or acetaminophen; and they precipitate withdrawal in narcotic-dependent patients. One of the newer drugs in this class, buprenorphine, has been shown to be clinically effective without marked psychotomimetic effects in patients with cancer, and to result in less physical dependence than morphine.29-31 Drugs in this class may offer special advantages to the management of pain from cancer.

Traditionally, the narcotic analgesics have been used to manage acute pain. Long-term use has been discouraged because of the development of tolerance,

physical dependence, and psychological dependence.³² Tolerance is a state in which escalating doses of drug are needed to maintain an analgesic effect. Physical dependence is characterized by the onset of acute symptoms and signs of withdrawal if the narcotic is suddenly stopped or a narcotic antagonist is administered. Psychological dependence or addiction, is separate from physical dependence and tolerance and is a concomitant behavioral pattern of drug abuse characterized by a craving for the drug and overwhelming involvement in obtaining and using it.

Because of the misconception by both clinicians and patients that physical dependence and addiction (psychological dependence) are interchangeable terms, the use of narcotic analgesics in patients with acute or chronic pain remains inadequate at best. This overriding fear of addiction coupled with physicians' lack of knowledge about the clinicopharmacologic properties of narcotic agents further limits effective use of them. 33-35 However, advances in our understanding of endogenous opiates in pain modulation and the plight of the patient with pain from cancer have led to a reevaluation of the role of narcotic analgesics in the management of chronic pain.

The long-term use of narcotic analgesics, administered orally, to manage cancer pain was heralded by the English hospice movement3,+ and has long been advocated in the care of patients dying from cancer. 32,36,37 Studies of the patterns of chronic narcotic drug use in patients with cancer and in those with other medical illnesses have demonstrated that tolerance and physical dependence occur but that psychological dependence (addiction) is rare. 38.39 This clinical experience with long-term narcotic drug use supports the concept that psychological dependence is separate from physical dependence.10 Drug use is not the sole factor in the development of psychological dependence; psychological, social, and economic factors also play a part. This observation has been supported by studies of heroin use by U.S. military personnel in Vietnam.40 The concept of "addiction" should be redefined in order to place the use of narcotic analgesics in perspective.41

Several reviews of oral and parenteral analgesics in the management of cancer pain provide guidelines for their use. 42-48 The American Medical Association and the American College of Physicians have outlined approaches to drug therapy in the management of severe chronic pain associated with advanced disease. Both groups have stressed the importance of providing adequate pain control and supportive care so that the patient can die relatively free of pain. They have also stressed the need to educate physicians and other health professionals in the care of patients with pain from cancer and in the use of narcotic analgesics.

Guidelines for the practical use of narcotic analgesics are presented in Table 4. Tables 5 and 6 list some of the important pharmacologic properties of the nonnarcotic and narcotic analgesics commonly used to

Table 4. Guidelines for the Use of Narcotic Analgesics in Pain Management,

- 1. Start with a specific drug for a specific type of pain.
- 2. Know the pharmacology of the drug prescribed.
 - 2. Duration of the analgesic effect.
 - b. Pharmacokinetic properties of the drug.
 - c. Equianalgesic doses for the drug and its route of administration (see Tables 5 and 6).
- 3. Adjust the route of administration to the patient's needs.
- 4. Administer the analgesic on a regular basis after initial titration of the dose.
- Use drug comminations to provide additive analgesia and reduce side effects (e.g., nonsteroidal antiinflammatory drugs, antihistamine [hydroxyzine], amphetamine [Dexedrine]).
- Avoid drug combinations that increase sedation without enhancing analgesia (e.g., benzodiazepine [diazepam] and phenothiazine [chlorpromazine]).
- 7. Anticipate and treat side effects,
 - a. Sedation.
 - b. Respiratory depression
 - c. Nausea and vomiting.
- d. Constipation.
- 3. Watch for the development of tolerance.
 - a. Switch to an alternative narcotic analgesic.
 - Start with one half the equianalgesic dose and titrate the dose for pain relief.
- 9. Prevent acute withdrawal.
 - a. Taper drugs slowly.
 - b. Use diluted doses of naloxone (0.4 mg in 10 ml of saline) to reverse respiratory depression in the physically dependent patient, and administer captiously.
- 10. Do not use placebos to assess the nature of pain.
- 11. Anticipate and manage complications.
 - a. Overdose.
 - b. Multifocal myocionus.
 - c. Seizures.

treat cancer pain. The guidelines are based in part on clinicopharmacologic principles and in part on the empirical use of these drugs in clinical practice. They serve as a useful reference point, but there remains a tremendous need to develop scientifically based guidelines.

Several controversies have arisen in the use of narcotic analgesics, including the best choice of an analgesic (e.g., morphine, methadone, or heroin), the route and schedule of administration (fixed or as needed), and the risk of psychological dependence with long-term use. 49 Although resolution of these controversies awaits controlled repetitive dosage studies, some of the available data are briefly reviewed below.

There is no "best choice" of analgesic agent but rather a series of agents, such as those listed in Tables 5 and 6, that have been used effectively to manage cancer pain. Oral morphine is the most commonly used drug, but its availability for outpatient pain management is severely restricted in developed and developing countries. For patients who cannot tolerate morphine, there are useful alternative drugs. Choosing the drug according to the needs of the individual patient is the rule. There may be pharmacokinetic reasons to choose shorter-acting drugs, such as morphine or hydromorphone, over methadone or levorphanol, if they are given on a fixed schedule. Accumulation of a toxic active metabolite, normeperidine, limits the long-term use of meperidine. It is the knowledge of pharmacologic properties that directs the choice of a drug. Attention to these considerations will ensure effective use of drugs.

Lack of knowledge of the equianalgesic doses of drugs, when a switch is made from one medication to another or from one route of administration to another, is the most common cause of undermedication. Because cross-tolerance is not complete, patients who become tolerant to the analgesic effect of one narcotic can be given another narcotic to provide better analgesia. 36,45 One half the calculated equianalgesic dose of the new drug is recommended for titrating the starting dose. This calculation is based on clinical experience and suggests that the relative potency of some of the narcotic analgesics, specifically those with long plasma half-lives, may increase with repetitive doses.

Lack of attention to the pharmacokinetic profile has also limited the effective use of certain drugs. The plasma half-lives of the narcotic analgesics vary widely and do not correlate with their analgesic time courses. Both methadone, with a half-life of 15 to 30 hours, and levorphanoi, with a half-life of 12 to 16 hours, produce analgesia for 4 to 6 hours. ^{50,51} With repeated doses, these drugs accumulate in plasma and can result in excessive sedation and respiratory depression. ^{52,53} It is necessary to adjust the dose and schedule according to the plasma half-life of the drug when it is introduced. ^{54,55}

Table 5. Oral Non-narcotic and Narcotic Analgesics for Mild to Moderate Pain.

	Dose (mg)*	DURATION (hr)	PLASMA HALF-LIFE (hr)	COMMENTS
Aspinn	650	4-6	3-5	Standard for non-narcotic comparisons; gastrointestinal and hematologic effects limit use in patients with cancer
Acetaminopoen	650	4-6	1-4	Weak antiinflammatory effects; safer than aspirin
Propoxyphene	651	4-6	12	Biotransformed to potentially toxic metabolite norpropoxyphene; used in combination with non-narcotic analgesics
Codeine	321	4-6	3	Biogramsformed to morphine; available in combination with non-narcotic analgesics
Meperidine	50	4-6	3-4	Biotransformed to active toxic metabolite normeperidine; associated with myoclonus and seizures
Pentazocine	30	4-6	2-3	Psychotomimetic effects with escalation of dose; only available in com- bination with naloxone, aspirin, or acetaminophen (U.S.)

^{*}Relative potency of drugs, as compared with that of aspina, for mild to moderate pain.

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^{*}Some investigators have reported that a much larger dose (propoxyphene, 130 mg; codeine, 60 mg) is effective in patients with mild to moderate pain.

Medication should be administered on a regular basis with the interval between doses based on the duration of the analgesic effect. The pharmacologic objective is to maintain the plasma level of the drug above a "minimal effective concentration for pain relief." ⁵⁶ However, the time required to reach a steady state after repeated administration depends on the half-life of the drug, and full assessment of the analgesic effica-

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cy of a drug regimen may thus take 24 hours, for a drug such as morphine, or up to five to seven days, for methadone. 34

The use of a combination of drugs enables the physician to improve pain relief without escalation of the narcotic dose. Several combinations have been proved effective, including a narcotic plus a non-narcotic (600 mg of aspirin or acetaminophen³⁶ or 400 mg of ibuprofen⁵⁷), a narcotic plus an antihistamine (100 mg of hydroxyzine given intramuscularly),⁵⁸ and a narcotic plus an amphetamine (10 mg of dextroamphetamine [Dexedrine] given intramuscularly).⁵⁹ Other drugs, which do not provide additive analgesia but

are commonly employed in combination with narcotic agents, include diazepam, chlorpromazine, and cocaine. 60-62

The Brompton Cocktail, which consists of varying doses of diacetylmorphine (heroin) or morphine, cocaine, phenothiazine, alcohol, and chloroform water, has been reported to control pain in 90 per cent of patients. Studies by Twycross have demonstrated that analgesic efficacy results from the narcotic alone and that morphine can be substituted for heroin. He has therefore advocated using oral narcotic solutions in titrated doses according to the needs of the individual patient rather than using cocktails. 3.63

The route of drug administration must also be selected according to the needs of the patient. The oral route is most practical, but the oral bioavailability of drugs varies widely. Recent studies have helped to establish a kinetic basis for the rational use of oral morphine and methadone in patients with cancer, 55,64-66 and have demonstrated that oral heroin, although effective as an analgesic, is inefficient as a means of

Table 6. Oral and Parenteral Narcotic Analgesics for Severe Pain.

	ROUTE*	DOSE (sig)†	DURATION	Plasma Half-Life (hr)	CONNENTS
Narcotic agonists					
Morphine	DM PO	10 60	4-6	2-3.5	Standard for comparison; also available in slow-release tablets
Codeine	IM PO	130 200\$	4-6	3	Biotransformed to morphine; useful as initial narcotic analgesi
Oxycodone	IM PO	15 30	3-5	_	Short acting; available alone or as 5-mg dose in combination wit aspirin and acetaminophen
Heroin	IM PO	5 60	4-5 4-5	0.5	Illegal in U.S.; high solubility for parenteral administration
Levorphanol (Levo-Dromoran)	DM PO	2 4	4-6	12-16	Good oral potency, requires careful titration in initial dosin because of drug accumulation
Hydromorphone (Dilaudid)	EM PO	1.5 7.5	4-5 4-6	2-3	Available in high-posency injectable form (10 mg/ml) for cache- tic patients and as rectal suppositories; more soluble that morphine
Oxymorphone (Numorphan)	IM PR	10	4-6	2-3	Available in parenteral and rectal-suppository forms only
Meperidine (Demerol)	IM	75	4-5	3-4 normeperidine	Contraindicated in patients with renal disease: accumulation active toxic metabolite normeperidine produces CNS excitation
Methadone (Dolophine)	IM PO	300‡ 10 20	4-6	12-16 15-30	Good oral potency; requires careful titration of the initial dose avoid drug accumulation
Mixed agonist- antagonist drugs					
Pentazocine (Talwin)	IM PO	60 180‡	4-6 4-7	2-3	Limited use for cancer pain; psychotomimetic effects with do- escalation; available only in combination with naloxone, aspirit or acetaminophen; may precipitate withdrawal in physically di- pendent patients
Nalbuphine (Nubain)	EM PO	10	4-6	5	Not available orally; less severe psychotomimetic effects that pentazocine; may precipitate withdrawal in physically depended patients
Butorphanol (Stadol)	IM PO	_2	4-6	2.5-3.5	Not available orally; produces psychotomimetic effects; may propietate withdrawal in physically dependent patients
Partial agonists					
Buprenorphine (Temgesic)	IM SL	0.4	4-6 5-6	7	Not available in U.S.; no psychotomimetic effects; may precip tate withdrawal in tolerant patients

^{*}IM denotes intramuscular, PO oral, PR rectal, and SL sublingual.

^{*}Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to as oral route. For patients without prior narcotic exposure, the recommended oral starting dose is 30 mg for methadone, 2 mg for inethadone, 2 mg for leverphanos, and 4 mg for hydromorphone.

IThe recommended starting doses for these drugs are listed in Table 5.

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delivering morphine.67 Several novel methods and routes of administration have been developed to maximize pharmacologic effects and to minimize undesirable effects associated with standard methods slow-release morphine tablets that are effective 8 to 12 hours. Novel routes under investigation in-clude intranasal, transdermal, and sublingual drug administration. The advantage of these routes is that they avoid drug metabolism by the liver (presystemic clearance), which substantially reduces the oral potency of morphine and some of the other narcotics. These alternative routes offer a special advantage, particularly in the patient with gastrointestinal obstruction, limited venous access, or reduced muscle mass. To date, only one drug, buprenorphine, is produced in a sublingual form, but it is not available in the United States.

Continuous infusions of narcotics by intravenous and subcutaneous routes have been employed to meet the needs of select populations of patients with cancer.58-71 Although the indications for these techniques, their limitations, and their efficacy have not been fully assessed and the pharmacokinetic basis for their use remains undefined, their clinical use is widespread and expanding. The inability to predict an ideal maintenance infusion rate and to accommodate differences among patients makes it difficult to use these techniques.72 The intravenous or oral equianalgesic doses are not known for many of the drugs. When a switch is made from the intramuscular route to continuous intravenous infusions, the starting dose is calculated as the equivalent morphine dose for a 24-hour period. This calculation is based on clinical experience, not controlled studies.47

Epidural and intrathecal administration of narcotics is based on the demonstration of opiate receptors in the dorsal horn and suppression of spinothalamictract neurons to noxious stimuli by opiates applied to the spinal cord. 73-78 Localized selective analgesia is produced without motor blockade. This approach minimizes the distribution of drugs to receptors in the brain stem and cerebral hemispheres, avoiding the side effects of systemic administration. The clinical efficacy of continuous infusions by this route, using the Infusaid pump, has been studied in patients with pain from cancer. The clinical and pharmacokinetic data demonstrate that profound analgesia can be produced with small doses of morphine. Because the dose and subsequent systemic uptake are much higher with epidural administration, the intrathecal route has been advocated. However, both epidural and intrathecal administration are associated with rostral redistribution of drug and central side effects. Also, tolerance occurs and is most problematic in the patient with progressive disease. Considerable cross-tolerance is induced by systemic narcotics, making it difficult to determine the proper timing for use of these techniques in the management of pain from cancer. Intraventricular administration of narcotics in patients with cancer has also been shown to provide profound analgesia when small doses of drug are administered through an Ommaya reservoir.⁷⁹

As noted above, tolerance occurs with long-term administration in patients with progressive disease, but increased doses of drug continue to produce analgesia, suggesting that with the narcotic agonist drugs there is no limit to tolerance. Tolerance of each of the effects of the narcotics occurs at a different rate. Switching to an alternative narcotic, adding non-narcotic agents, and employing neurosurgical and anesthetic approaches are methods commonly used to manage pain in the patient with a tolerance to a particular narcotic agent.

These guidelines notwithstanding, the management of pain with analgesics remains difficult. Much of the difficulty encountered arises from differences in the responses of individual patients to the same dose of drug. Kaiko and colleagues have described some of the sources of variation in the responses of patients with cancer to morphine and the need for dose adjustment on the basis of age. 80.81 The efficacy of such drugs is based on an understanding of their clinicopharmacologic properties and improved methods to manage their side effects. Effective use of narcotic agents is now possible because of the development of specific and sensitive techniques to quantitate drugs in biofluids, the availability of well-defined clinical methods to measure the pain response, and the application of pharmacokinetic and pharmacodynamic models to relate plasma concentrations of narcotics to analgesic effects. 82.83 Recent studies demonstrate that equianalgesic doses of heroin are comparable to morphine in their analgesic effect, side effects, and influence on mood. These studies refute anecdotal reports of heroin's superiority. 84 Studies of repeated meperidine administration in patients with cancer have demonstrated that central nervous system hyperirritability results from accumulation of the active toxic metabolite, normeperidine.85

Adjuvant Analgesic Drugs

Adjuvant analgesic agents constitute a third group of drugs used to treat patients with pain from cancer. 36,87 This group includes several different categories of drugs, such as anticonvulsant agents,88 phenothiazines,89 butyrophenones,90 tricyclic antidepressants.91,92 antihistamines, amphetamines, and steroids93,94 and levodopa.95 These drugs produce analgesia in certain painful states by mechanisms not clearly established and not directly related to the opiate receptor system. Clinical interest in their use has developed from a greater understanding of the neuropharmacologic characteristics of pain and the ability of these drugs to enhance or block neurotransmitter function. In some instances, analgesic effects have been established in controlled clinical trials, such as the use of amitripty-line in postherpetic neuralgia, 91 but for most of these drugs, anecdotal data or clinical surveys provide the rationale for their use, which is controversial at best. Although these drugs are commonly used in patients with pain from cancer, the evidence suggests that they are not as effective as narcotic analgesics in relieving pain. Adjuvant analgesic drugs have been developed and released for clinical indications other than pain relief.

Anesthetic Approaches

These approaches are most useful in treating patients with well-defined localized pain from tumor infiltration. Short-acting and long-acting anesthetics are used for temporary and diagnostic nerve blocks, whereas phenol, alcohol, and freezing (cryoanalgesia) are the common neurolytic agents used for permanent blocks. 96-99 The principal pathologic effect produced by these agents is demyelination, with secondary nerve degeneration. Local freezing causes a loss in nerve function, which reportedly lasts for several weeks only.99 A permanent nerve block is performed if a temporary block has demonstrated efficacy. The most common indications for nerve block are listed in Table 3. The limitations of these procedures are that each peripheral nerve subserves sensory function over multiple levels, requiring multiple nerves to be blocked for adequate pain control. Similarly, epidural and intrathecal nerve blocks with neurolytic agents can produce motor weakness and autonomic dysfunction. The techniques, indications, and diluent and concentration of neurolytic agents vary from investigator to investigator, with satisfactory results reported in 22 to 80 per cent of patients and permanent side effects, such as urinary or rectal incontinence, motor weakness, or paresthesias, in 1 to 13 per cent. 96-102 However, the use of autonomic nerve blocks, such as celiac-plexus block, to manage midabdominal pain associated with carcinoma of the pancreas is very effective in 60 per cent of patients and is often the procedure of choice in such patients. 101

Intermittent or continuous epidural infusions of local anesthetics have been used for temporary management of the difficult pain syndromes involving the lumbosacral plexus and sacrum. By varying the amount and concentration of the local anesthetic delivered continuously by an infusion pump or intermittently by a subcutaneously implanted reservoir attached to a catheter placed in the epidural space, pain relief can be achieved without interruption of motor or autonomic function. 103 The advantage of this method is that it does not result in cross-tolerance with opiate analgesia, and temporary use of epidural infusions allows for a reduction in the amount of systemic opiate drugs, partially reversing tolerance. This is a useful preliminary approach to reduce tolerance when spinal opiate analgesia is under consideration as a therapeutic approach.

Two anesthetic approaches used to manage diffuse pain are chemical hypophysectomy and intermittent inhalation therapy with nitrous oxide. Chemical hypophysectomy, which involves the injection of alcohol into the sella turcica under radiologic supervision, is used to control pain in patients with widespread bony metastases. Initial studies reported dramatic pain relief in 60 per cent of 600 patients, but more recent studies report relief in 35 to 74 per cent of patients. 104.105 The mechanism of analgesia may be related in part to the tracking of alcohol up the pituitary stalk and the consequent disruption of the hypothalamic—thalamic endorphinergic pain pathway. The lack of detailed clinical data and information on the endocrine status of such patients limits critical assessment of the technique, and in many patients pain relief occurs independently of tumor regression.

Nitrous oxide is used to manage chronic pain from tumor progression or pain in the dying patient. ¹⁰⁶ It is administered in oxygen through a nonrebreathing face mask, with concentrations ranging from 25 to 75 per cent, often in combination with systemic narcotics. Patients can remain alert during its use. It is most useful in managing acute incident pain and procedure-related pain.

Lastly, trigger-point injections. 107 although considered an anesthetic procedure, are commonly used in clinical practice and require no special expertise. A focal injection of saline or local anesthetic into a painful muscle joint provides dramatic relief. However, a careful assessment of the nature of the pain should be undertaken.

Neurosurgical Approaches

At present, cordotomy and placement of epidural, intrathecal, and intraventricular catheters for narcotic drug delivery are the most common neurosurgical procedures performed for pain relief (Table 2).108-115 A cordotomy involves the interruption of the anterior lateral spinothalamic tract in the cervical or thoracic region. It may be performed as a percutaneous stereotactic procedure or by an open surgical approach. It is most useful in managing unilateral pain below the waist. Initial complications include paresis in 5 per cent of patients, ataxia in 20 per cent, and urinary dysfunction in 10 per cent, with late complications occurring in only 5 per cent. Although initial pain relief from cordotomy occurs in 90 per cent of patients, this figure drops to 80 per cent at three months, and at the end of one year approximately 40 per cent of patients report a return of pain. Another limiting factor in the success of both open and percutaneous cordotomies is that pain develops on the side opposite the cordotomy site in 7 to 10 per cent of patients; even more distressing, in a comparable number of patients, pain previously unrecognized at another site becomes as intractable as the pain for which the cordotomy was performed. This is one of the most common causes for the failure of cordotomy and explains the limited usefulness of the procedure in patients with diffuse pain.

Each of the other neurosurgical procedures involves either sectioning or stimulation of the peripheral Vol. 313 No. 2

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BEHAVIORAL APPROACHES

Behavioral approaches, including relaxation training, biofeedback and cognitive and behavioral training, hypnosis, and music therapy, have been integrated into the management of cancer pain. 116-121 The major goal of these interventions is to promote an increased sense of control by reducing the hopelessness and helplessness that many patients with pain from cancer experience. These techniques also serve as a calming diversion of attention, breaking the painanxiety-tension cycle. The effectiveness of any one of these techniques, as compared with another or with standard medical or surgical therapy, is unknown, and few controlled studies have been performed. Patients are taught these techniques and then use them independently. Relaxation training can be given by all health care professionals, whereas other approaches require biophysical instrumentation or more specialized skills. Cognitive and behavioral training provides patients with a variety of strategies to divert their attention away from pain, facilitate their tolerance of pain, and increase their perceived self-control and adaptive functioning.

Music therapy has been used in hospitals and hospice settings either alone or in combination with relaxation training and hypnosis to augment the effects of these techniques. ¹¹⁹ Hypnosis has been studied the most extensively and has been widely used in the treatment of acute and chronic cancer pain. ^{120,121} Studies report that 50 per cent of patients may obtain some pain relief, yet indicate that there is no single effective hypnotic procedure.

In general, these behavioral techniques reduce pain by means of mechanisms that are in part related to their ability to modulate the affective response to painful stimuli. Studies have demonstrated that analgesia induced by hypnosis is not mediated by the endogenous opiate system, because it is not reversed by naloxone. 122

SUPPORTIVE CARE

Numerous models of supportive care have stressed the importance of pain control for the patient at home. Inadequate control of pain in the outpatient is a common cause for readmission to the hospital. Specific guidelines for managing cancer pain at home include education of patients, their families, and health care professionals in the proper use of analgesics; 24-hour availability of a physician or a nurse with expertise in pain management to adjust drug doses; adequate drug supplies for alternative routes of administration, such as the parenteral route; and education in the use of naloxone to reverse opiate-induced respiratory depression.

These approaches, coupled with psychological support for patients and their families and integration of social services, can give the patient with pain the option to remain at home, 3.4.123,124

SUMMARY

Pain is one of the most feared consequences of cancer. Control of pain from cancer should be possible with the approaches discussed above. Changing attitudes toward the effective use of narcotic analgesics, the development of novel routes and methods of administration, and a clinical approach based on scientific principles and humane care offer the promise of improved management of pain in patients with cancer.

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Massachusetts Medical Society Registry on Continuing Medical Education

To obtain information on continuing medical education courses in the New England area, write or call, indicating field(s) or specialty in which information is desired, to the Committee on Medical Education, 1440 Main St., Waltham, MA 02254; telephone (617) 893-4610 (Metropolitan Boston) or WATS 1-800-322-2303 (Massachusetts).

Indicates changes requested by DDMAC

Indicates change made by Purdue Pharma after initial DDMAC review

CONFIDENTIAL PURCHI-000623032



CONFIDENTIAL PURCHI-000623033

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

New ql2h Warning-May be habit forming

larger

The one to start with

The logical "next step" for patients no longer tolerating or responding to nonopioids

- Paint legins within 1 hour in most patients—pain control lasts 12 hours

- Less frequent dosing than with Percocet*, Vicodin*, or Tylenol* with Codeine

The one to stay with.

- No "ceiling" to analgesic efficacy—may be titrated upward when clinically necessary
- Patients avoid the added risk of gastric/hepatic/renal toxicity that can result from

maximal -high daily doses of ASA or APAP

Excellent compliance, high degree of patient acceptability during clinical trials

Easy to live with.

- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Common opioid side effects may be anticipated and effectively managed or prevented; many diminish over time for most patients, except for constipation

Easy to dose.

 Small, color-coded tablets are easy to identify and swallows an important benefit for patients on multiple medications.



- Variety of strengths permit precise titration to an effective dose
- Manage breakthrough or incident pain with IR oxycodone to avoid polypharmacy

g including Oxy Contin.

OxyContin" The longest-lasting oxycodone ever.

J Around- Hie-Clocko

figer from so accompany work

CONFIDENTIAL PURCHI-000623034 The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyContin Titration Guide

	OxyContin Tablets q12h dose	IR oxycodone	,
_	10 mg q12h	5 mg pre	7.5 GH077947
Ö	20 mg q12h	5mg pen.e	Day Contin
10 mg	30 mg q12h	10 mg pm-(-	Titrate the dose if more than two rescue doses per day are
③	40 mg q12h	10 mg prayt	
20 mg	60 mg q12h	15 mg pan-	needed.
0	80 mg q12h	20 mg sm.e.	65
40 mg	120 mg q12h	30 mg pen A	
	Continue titrating, if necessary	y, using the T+I+M+E-principles belo	ow.

Titrate patients every 1-2 days, if necessary.

Increase the dose by 25%-50%, if necessary do not increase the dosing frequency.

Manage breakthrough pain with IR oxycodone 43.44 per at 1/4 to 1/3 of the 12-hour OxyContin dose.

Elevate the OxyContin dose if more than two rescue doses are required per day.

f*For patients taking OxyContin 10mg q12h...

- The next titration step should be 20mg q12h
- Breakthrough pain should be managed with IR oxycodone 5mg/

New ql2h

OXYCODONE HCI CONTROLLED-RELEASE) TABLETS

Purper Warning—May be habit formin



Small, color-coded tablets (actual siz

Numr Phase see occompanying Language information.

17

Note from Kilmerye.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin[®]

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For around-the-clock pain: OxyContin CII

10 mg q12h

If a nonopioid analgesic is being taken, it may be continued.

For supplemental analgesia:

Immediate-Release (IR) Oxycodone

5 mg administered 1 hour before anticipated incident pain

5 mg administered q3 4h pm/ for breakthrough pain (if needed)

Note: If more than two rescue doses are needed per day, OxyContin should be titrated upward.

Converting to OxyContin.

Fixed-Combination Opioid/
Nonopioid Products

OxyContin

Dose of regular-strength products (eg, Percocet*, Percodan*, Tylox*, Vicodin*, Lortab*, Lorcet*, or Tylenol* With Codeine)	Recommended OxyContin conversion dose range	IR oxycodone rescue dose for breakthrough paint
1-5 Tablets/Capsules/ Caplets per day	10-20 mg q12h	5 mg q3-4h pm
6-9 Tablets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg q3-4h pm •
10-12 Tablets/Capsules/ Caplets per day	30-40 mg q12h	10 mg q 3-4h pm 2

Note: The nonopioid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opioids when initiating OxyContin therapy.

* See professional prescribing information for immediale-release oxycodone

Warning: Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS Sections If in professional prescribing information.

CONFIDENTIAL

EASY TO LIVE WITH.

The AHCPR, in Management of Cancer Pain, recommends that side effects be treated aggressively...

Constipation: is a common problem; associated with opioid administration.

[II] can usually be managed by an increase in fiber consumption and the use of a mild loxalive. If more severe, it can be ireated with a stimulating cathortic drug tergy, esennal concentrate.

It more severe, it can be ireated with a stimulating cathortic drug tergy, esennal concentrate.

It more severe, it can be ireated with a stimulating cathortic drug tergy, esennal concentrate.

It more severe, it can be ireated within a stimulation of increased stimulating cathortic developes reported in a stimulation of increased substantially but to leave to the increased and vomiting. As with other side effects, this important to determine the cause of increased with a little market extension of the increased with a little market extension of the increased with a little market extension of the increased with a little market extension.

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PURCHI-000623037

THE ONE TO STAY WITH.

In cancer studies'...

- Titration enhanced efficacy of therapy—only 3.5% of cancer patients discontinued (due to inadequate pain control) when allowed to titrate and use rescue medication
- Patients were titrated as quickly and easily with OxyContin as with immediate-release oxycodone
- 92% of patients were titrated to stable pain control with OxyContin
- Average time to stable pain control was 2 days

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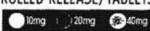
100% of OxyContin patients were dosed q12h

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Warning—May be habit forming



Small, color-coded tablets (actual size)

ANTIN Please see accompanying the prescribing information.

13

OxyContin[®]

 \mathbf{E}

Common opioid side effects; many diminish over times

Adverse experiences reported over time by concer patients (n=86)*

Drug-related ADE	Week 1 (%)*	Week 5 (%)*	Week 10 (%)*
Nausea	20	12	4
Sedation	14	8	8
Dry Mouth	9	0	. 0
Vomiting	8	7	0
Proritus	7	0	0
Dizziness	5	5	0

What I teres of potent reporting ADE once or more during specified week of OnyCordin theory

- The most serious risk associated with opioids is respiratory depression

 A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study (P<0.0001)

- Most side effects diminished over time, even as daily doses increased

- except for constipations

 Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness

"Copies, Forts, Crophon, et al. Decrease in epicid-wholed orderne experiences (AE) during chronic therapy with controlled-veloces conjugate (CryCI) in concer para parliam. These read as the American Para Society, Newscher, 1995, los Angeles, CA.

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THE ONE TO STAY WITH.

A single-entity agent-dose not limited by ASA or APAP "ceilings."

		Maximum Recommended Delly Dase of Nonopiold	
Product (opicid/nonopioid ratio [mg])	Nonopioid Ingredient	Goodman Signal & Gilman	Regimen Shoold Not Exceed
OxyContin™	N/A	A PROPERTY OF	N/A
Percoce# (5/325)	APAP	4 7.5740 s 44.44	12 tobs/day
Percodon® (5/325)	ASA		16 tobs/day
Ty'cx** (5/500)	APAP	40 5	8 labs/day
Vicadin* (5/500)	APAP	40	8 tobs/day*
Vicedin* ES (7.5/750)	APAP	10 × 10	5 tobu/day*
Lorce(*HD (5/500)	APAP	Canal To Car San	8 tobs/day
Lorcer* (10/650)	APAP	(0)	6 tabe/day*
lancb* (2.5/500)	APAP	100	8 labs/day*
lenob* (5/500)	AFAP	S C	8 tobs/day*
Lortab* (7.5/500)	APAP	(中国中国 10 国 E PA A F	6 tabs/day*
Lorisb* ASA (5/500)	ASA	# 200 CO SUCCES	8 tabs/day*
Tylenol* with Codeine No. 2 (15/300) No. 2 (30/300) No. 4 (66/300)	APAP APAP APAP	19 10 10 10 10 10 10 10 10 10 10 10 10 10	13 tabs/day* 12 tabs/day* 6 tabs/day*



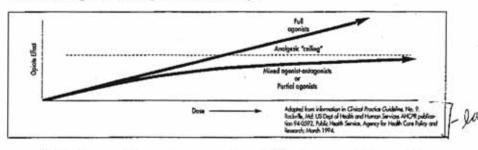




CONFIDENTIAL PURCHI-000623040

OxyContin[®]

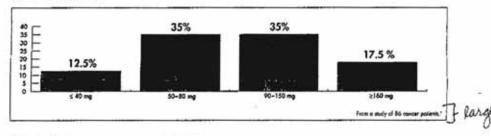
No ceiling to analgesic efficacy.



 With full agonists, such as oxycodone, "effectiveness with increasing doses is not limited by a 'ceiling'." *

OxyContin may be dosed upward as clinically necessary.

Percent of cancer patients receiving various daily doses of OxyContin at the end of a 12-week trial.



Ideal for long-term opioid therapy

 A single-entity oral agent—contains no APAP or ASA; allows independent coadministration and dosage adjustments with nonopioid of choice

ACROCONTIN® Delivery System.

The OxyContin™CII (oxycodone HCl controlled-release)
Tablets Dual Action Delivery System.

Dissolution

Gastrointestinal fluids dissolve tablet surface, exposing hydrophobic/acrylic matrix. Initial quantities of oxycodone are released on contact with GI fluids which channel through the tablet.

Diffusion/Dissolution

Active drug substance begins to diffuse through hydrophobic/acrylic matrix, becoming available for prolonged absorption.

Special patented polymer/acrylic matrix of the delivery system renders OxyContin Tablets "pH independent," allowing uniform release within an acid environment (the stomach) or an alkaline environment (the intestines).

"pH independence" assures...

Minimal effect of stomach contents on absorption—bioavailability unaffected by food.

piofeo

Please see accompanying the prescribing information. I larger

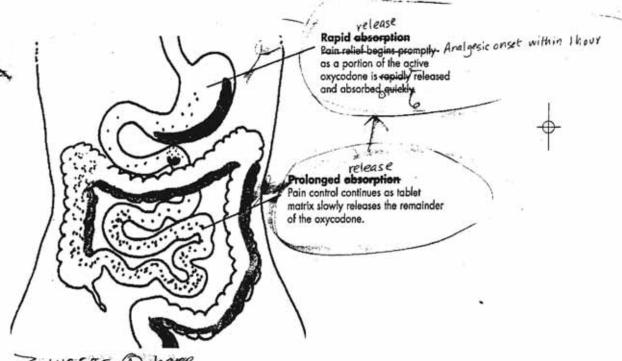
Proc. Royalti James of gran

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

The 12-hour

ACRO

Improved Contin[®] delivery system allows both rapid and prolonged absorption. release



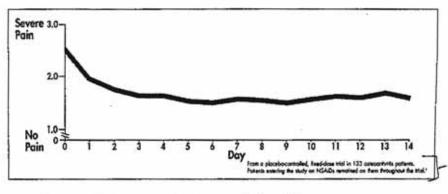
100% of OxyContin patients in clinical trials were dosed q12h

CONFIDENTIAL PURCHI-000623043

THE ONE TO START WITH.

(A-T-C).

Q12h dosing provides smooth and sustained pain control.



- Prompt reduction in pain intensity over the first 24 hours
- By Day 3, patients had achieved 94% of their total pain reduction
- Patients reported that OxyContin did not impair their ability to...
 - -Sleep
- Perform normal work
- -Get along with other people

- Walk
- -Enjoy life

100% of OxyContin patients were dosed q12h

New qi2h



In this study, Oxy Contin 20mg 912h...
- Significantly decreased pain
- Improved quality of life; mood and sleep

OxyContin[®]

Prompt onset of relief:

Analgesic action within 1 hour in most patients.

1 hour

Percent of patients experiencing onset of pain relief.

90%

Parger From a single-down and paragraphic onset with

Analgesic onset within I hour

Prompt-pain relief plus a longer duration of action than Percocet*,
 Vicodin*, or Tylenol* with Codeine

garger

"Sunaione PD. Ornet, peck, and duration of analgesia using the scring technique: a comparison of controlled-visions exposione in communications and in combination with australinaphes. American Pain Society Program Soci. 1994; A36, F94607 (Abornot)

OxyContin clinically studied in various pain syndromes

- More than 10 clinical trials
- More than 700 patients with either cancer or noncancer pain
- 100% of patients receiving OxyContin were dosed q12h

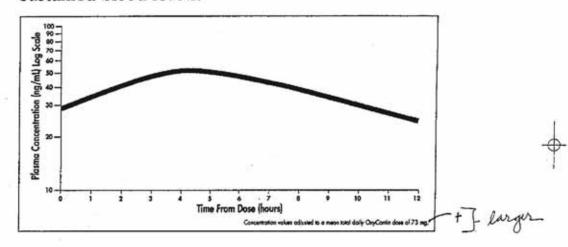
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PURCHI-000623045

THE ONE TO START WITH.

Q12h dosing provides smooth and sustained blood levels.



Fewer "peaks and valleys" than with immediate-release oxycodone

1 100% of OxyContin patients were dosed q12h

Darwer + Around - the -clock o

New q12h

OXYCONTIN

(OXYCODONE HCI CONTROLLED-RELEASE) TABLETS

Parger - [Warning-May be habit forming

10mg () 20mg



professional

ase see accompanying 😂 prescribing information

Small, color-coded tablets (actual size

CONFIDENTIAL

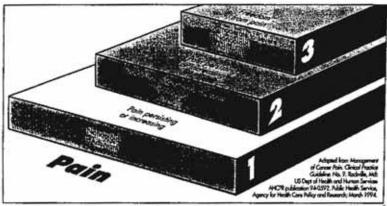
PURCHI-000623046

OxyContin[®]

I with persistent pains

The logical next step for patients no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



around-the-clock (A-T-C)

maximal

Q12h OxyContin-ideal for initial opioid therapy.

 Twelve hours of smooth and reliable pain control—less frequent dosing than with short-acting products such as Percocet*, Percodan*, Tylox*, Vicodin*, Lortab*, Lorcet*, and Tylenol* with Codeine

Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox

- Patients are spared the added potential toxicities of high daily doses of ASA or APAP
- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Patients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percodon is a registered trademark of The De PostMerck Pharmaceutical Co. Tylos is a registered trademark of Michiel Pharmaceutical Inc. Local is a registered trademark of UAD laboratories.

T

PURCHI-000623047

CONFIDENTIAL

For patients with moderate to severe pain requiring opioid therapy for more than a few days,

Introducing New q12h OXYCONTIN (OXYCODONE HCI CONTROLLED-RELEASE) TABLETS Warning—May be habit forming)

garger

maximal

The analgesic efficacy of immediate-release oxycodone The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet*, Vicodin*, or Tylenol* with Codeine

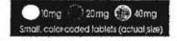
Prompt onset of relief analgesic action within 1 hours in most patients

Single-entity agent—contains no aspirin or acetaminophen which may be potentially toxic in high daily doses

No "ceiling" to analgesic efficacy-may be fitrated upward when clinically necessary

Common opioid side effects — often

diminishing over time for many patients,



OxyContin Tablets are to be taken whole. Taking broken, cherved or crushed tablets could lead to the rupid release and absorption of a patentially tank does of anycodone. The most serious risk associated with opiologic demonstrating respiratory depression. Commo opioid side effects are constitution, nousea, sedation, distincts, varniting, parities, beadache, dry mouth/sweeting, and weakness.

Percost is a registered trademark of the **Definitifient** Pharmacentral Co Yacolin a a registered trademark of Krall Pharmaceuroa' Company. Tyrenal with Codema is a registered trademark of McNeil Pharmaceutral

OxyContin"

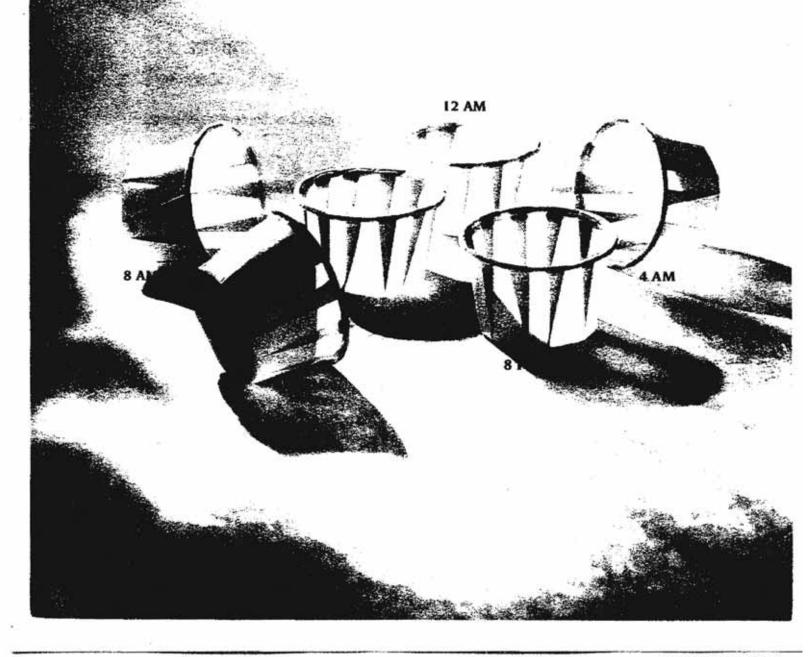
The longest-lasting oxycodone ever.

garger [Please see accompanying bet prescribing information.

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CONFIDENTIAL

24 Hours Of Oxycodone Pain Control THE OLD WAY



New q12h OXYCODONE HCL CONTROLLED-RELEASE) TABLETS Warning—May be habit.

The one to start with (A-T-C).

- The logical "next step" for patients, with persistent pain, no longer tolerating or responding to nonopioids
- Analgesic onset within 1 hour in most patients—pain control lasts 12 hours
- Less frequent dosing than with Percocet*, Vicodin*, or Tylenol* with Codeine

The one to stay with.

- No "ceiling" to analgesic efficacy-may be titrated upward when clinically necessary
- Patients avoid the added risk of gastric/hepatic/renal toxicity that can result from maximal daily doses of ASA or APAP
- Excellent compliance, high degree of patient acceptability during clinical trials

Easy to live with.

- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Common opioid side effects may be anticipated and effectively managed or prevented; many diminish over time for most patients, except for constipation

Easy to dose.

Small, color-coded tablets are easy to identify and swallow



- Variety of strengths permit precise titration to an effective dose
- Manage breakthrough or incident pain with IR oxycodone to avoid polypharmacy

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

OxyContin[™] The longest-lasting oxycodone ever.

* Around-the-clock.

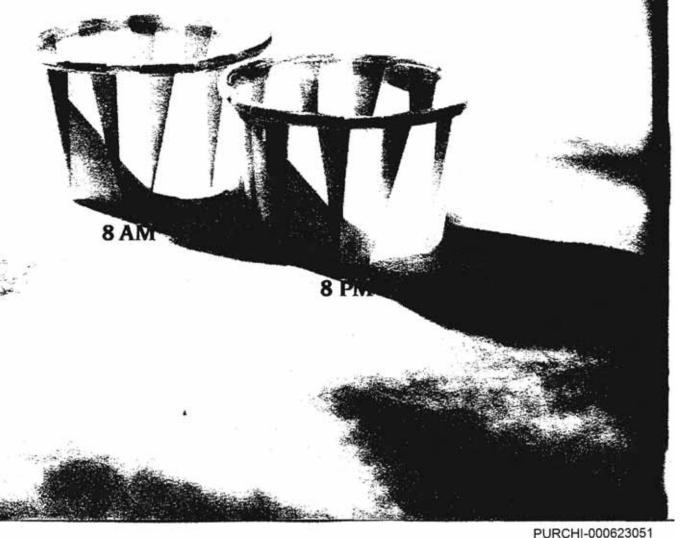
Please see accompanying professional prescribing information.

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CONFIDENTIAL PURCHI-000623050

Hours Of Oxycodone Pain Consideration Consid



For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Introducing New q12h OXYCODONE HCI CONTROLLED-RELEASE) TABLETS Warning—May be habit forming

The analgesic efficacy of immediate-release oxycodone The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet*, Vicodin*, or Tylenol* with Codeine

Analgesic onset within 1 hour-in most patients

Single-entity agent—contains no aspirin or acetaminophen which may be potentially toxic in maximal daily doses

No "ceiling" to analgesic efficacy—may be titrated upward when dinically necessary

Common opioid side effects—often diminishing over time for many patients, except for constipation



OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

Percocet is a registered trademark of The DuPont Merck Pharmaceutical Co. Vicodin is a registered trademark of Knoll Pharmaceutical Company. Tylenol with Codeine is a registered trademark of McNeil Pharmaceutical.

OxyContin[™] The longest-lasting oxycodone ever.

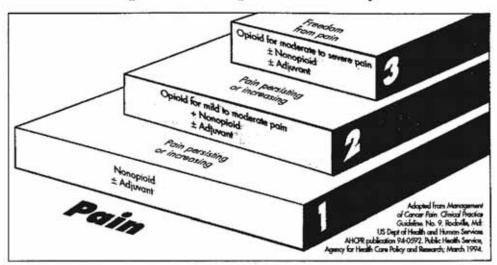
Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyConti

The logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



Q12h OxyContin—ideal for initial around-the-clock (A-T-C) opioid therapy.

 Twelve hours of smooth and reliable pain control—less frequent dosing than with short-acting products such as Percocet*, Percodan*, Tylox*, Vicodin*, Lortab*, Lorcet*, and Tylenol* with Codeine

Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox

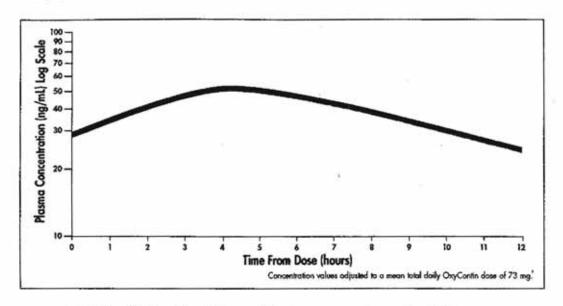
- Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP
- Convenient q12h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
- Patients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percodan is a registered trademark of The DuPont Merck Pharmaceutical Co. Tylox is a registered trademark of McNeil Pharmaceutical. Lortab is a registered trademark of Whitby Pharmaceuticals Inc., Lorcet is a registered trademark of UAD Laboratories.

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THE ONE TO START WITH (A-T-C).

Q12h dosing provides smooth and sustained blood levels.



100% of OxyContin patients were dosed q12h

*Around-the-clock.
†Data on file, Purdue Pharma L.P.





Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyConti

Analgesic onset within I hour in most patients.



Percent of patients experiencing analgesic onset.



From a single-dose study."

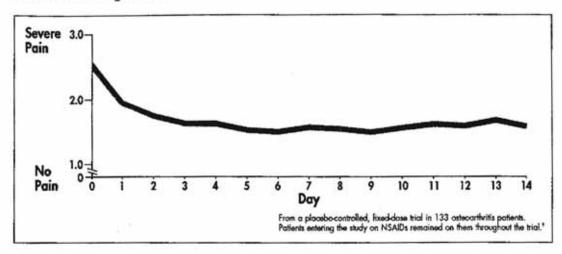
- Analgesic onset within 1 hour plus a longer duration of action than Percocet*, Vicodin*, or Tylenol* with Codeine
- *Sunshine A. Onset, peak, and duration of analgesic effect using the sorting technique: a comparison of controlled-release oxycodone v. immediate release oxycodone alone and in combination with acetaminophen. American Pain Society Program Book. 1994; A-36, #94607 (Abstract).

OxyContin clinically studied in various pain syndromes

- More than 10 clinical trials
- More than 700 patients with either cancer or noncancer pain
- 100% of patients receiving OxyContin were dosed q12h

THE ONE TO START WITH (A-T-C).

Q12h dosing provides smooth and sustained pain control.



- Prompt reduction in pain intensity over the first 24 hours
- By Day 3, patients had achieved 94% of their total pain reduction
- In this study, OxyContin 20mg q12h...
 - Significantly decreased pain
 - Improved quality of life, mood and sleep

100% of OxyContin patients were dosed q12h

[†]Roth S, Burch F, Fleischmann R, et al. The effect of controlled-release (CR) oxycodone on pain intensity and activities in patients with pain secondary to osteoarthritis. Presented at the American Pain Society, November, 1995, Los Angeles, CA.



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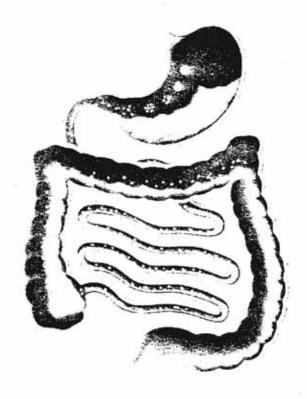
Please see accompanying professional prescribing information.

10mg 20mg 40mg Small, color-coded tablets (actual size) For patients with moderate to severe pain requiring opioid therapy for more than a few days.

The 12-hour

Improved Contin[®] delivery system allows both rapid and prolonged release.

Rapid release Analgesic onset within 1 hour as a portion of the active oxycodone is released and absorbed.



Prolonged release

Pain control continues as tablet matrix slowly releases the remainder of the oxycodone.

"pH independence" assures...
Minimal effect of stomach contents on absorption—bioavailability unaffected by food.

100% of OxyContin patients in clinical trials were dosed q12h

ACROCONT A Delivery System.

The OxyContin™CII (oxycodone HCl controlled-release) Tablets Dual Action Delivery System.

Dissolution

Gastrointestinal fluids dissolve tablet surface, exposing hydrophobic/acrylic matrix. Initial quantities of oxycodone are released on contact with GI fluids which channel through the tablet.

Diffusion/Dissolution

Active drug substance begins to diffuse through hydrophobic/acrylic matrix, becoming available for prolonged absorption.

Special patented polymer/acrylic matrix of the delivery system renders OxyContin Tablets "pH independent," allowing uniform release within an acid environment (the stomach) or an alkaline environment (the intestines).

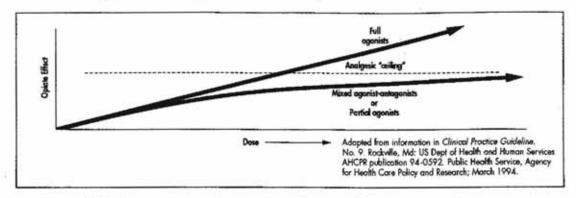
OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.

Please see accompanying professional prescribing information.

For patients with moderate to sorere pain requiring opioid therapy for more than a few days.

OxyCont

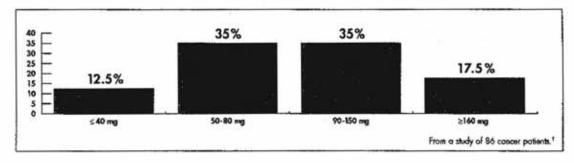
No ceiling to analgesic efficacy.



 With full agonists, such as oxycodone, "effectiveness with increasing doses is not limited by a 'ceiling'."*

OxyContin may be dosed upward as clinically necessary.

Percent of cancer patients receiving various daily doses of OxyContin at the end of a 12-week trial.



Ideal for long-term opioid therapy

 A single-entity oral agent—contains no APAP or ASA; allows independent coadministration and dosage adjustments with nonopioid of choice

THE ONE TO STAY WITH

A single-entity agent—dose not limited by ASA or APAP "ceilings."

Maximum Recommended Daily Dose of Nanopioid

Product (opioid/nonopioid ratio [mg])	Nonopioid Ingredient	Goodman & Gilman‡	Regimen Should Not Exceed
OxyContin™	N/A	N/A	N/A
Percocer* (5/325)	APAP	4 G	12 tabs/day
Percodon® (5/325)	ASA	6 G	18 tabs/day
Tylan [®] (5/500)	APAP	4 G	8 tabs/day
Vicodin* (5/500)	APAP	4 G	8 tabs/day*
Vicodin® ES (7.5/750)	APAP	46	5 tabs/day*
Lorce#-HD (5/500)	APAP	4 G	8 tabs/day
Lorcer* (10/650)	APAP	4 G	6 tabs/day ^t
Lortob* (2.5/500)	APAP	46	8 tabs/day1
Loriob* (5/500)	APAP	4 6	8 tabs/days
(7.5/500)	APAP	46	6 tabs/days
Lortob® ASA (5/500)	ASA	6 G	8 tabs/day*
Tylenol* with Codelne No. 2 (15/300) No. 3 (30/300) No. 4 (60/300)	APAP APAP APAP	4 G 4 G 4 G	13 tobs/day* 12 tobs/day* 6 tabs/day*

^{*} Management of Cancer Pain: Adults. Clinical Practice Guideline. Quick Reference Guide for Clinicians. Rockville, Md: US Dept of Health and Human Services AHCPR publication 94-0593. Public Health Service, Agency for Health Care Policy and Research; March 1994.

Physicians' Desk Reference. 49th ed. Montvale, NJ: Medical Economics Data; 1995:[see respective product names]. New ql2h

OXYCODONE HCI CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

Please see accompanying professional prescribing information.



[†] Kaplan R, Parris W, Croghan M, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

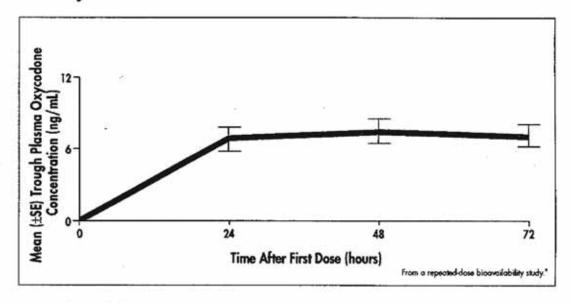
[‡]Insel PA. Analgesic-antipyretics and antiinflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In: Goodman LS, Gilman A, eds., The Pharmacological Basis of Therapeutics. New York, NY: McGraw-Hill, Inc.; 1990:638-681.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin

Easy to titrate:

Steady-state blood levels achieved in 24-36 hours.



 If needed, pain assessment and titration may be carried out every 1 to 2 days—especially important for patients with rapidly escalating pain

^{*}Reder R, Kaiko R, Grandy R, et al. Steady-state bioavailability comparison of controlled release oxycodone (OxyContin) tablets vs. axycodone oral liquid. American Pain Society Program. 1994; A-36, #94604 [Abstract].

THE ON

In cancer studies ...

- Titration enhanced efficacy of therapy-only 3.5% of cancer patients discontinued (due to inadequate pain control) when allowed to titrate and use rescue medication
- Patients were titrated as quickly and easily with OxyContin as with immediate-release oxycodone
- 92% of patients were titrated to stable pain control with OxyContin
- Average time to stable pain control was 2 days

† Data on file, Purdue Pharma L.P.

100% of OxyContin patients were dosed q12h











basy to timate

Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin

Common opioid side effects; many diminish over time, except for constipation.

Adverse experiences reported over time by cancer patients (n=86)*					
Drug-related ADE	Week 1 (%)^	Week 5 (%)^	Week 10 (%)*		
Nausea	20	12	4		
Sedation	14	8	8		
Dry Mouth	9	0	0		
Vomiting	. 8	7	0		
Pruritus	7	0	0		
Dizziness	5	5	0		

A Percent of patients reporting ADE once or more during specified week of OxyContin therapy.

- The most serious risk associated with opioids is respiratory depression
- A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study (P<0.0001)
- Most side effects diminished over time, except for constipation, even as daily doses increased
- Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness

^{*}Kaplan R, Parris W, Croghan M, et al. Decrease in opioid-related adverse experiences (AE) during chronic therapy with controlled-release oxycodone (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Angeles, CA.

EASY TO LIVE WITH.

The AHCPR, in Management of Cancer Pain, recommends that side effects be treated aggressively...

"Constipation is a common problem associated with opioid administration.

(It) can usually be managed by an increase in fiber consumption and the use of a mild laxative...." If more severe, it can be treated with a "stimulating cathartic drug, e.g.,...senna concentrate."

"Transitory **sedation** is common when opioid doses are increased substantially, but tolerance usually develops rapidly."

Nausea and vomiting. "As with other side effects, it is important to determine the cause. Clinical experience suggests that opinid-induced nausea and vomiting can be managed with antiemetics chosen according to their modes of action."

From Management of Concer Point. Clinical Practice Guideline. No. 9. Rackville; Mck. U.S. Dept of Health and Human. Services AHCPR publication 94-0592; Public Health Service, Agency for Health Care Policy and Research; March 1994.

New ql2h

OXYCODONE HCI CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming



Small, color-coded tablets (actual size)

Please see accompanying professional prescribing information.

For patients with moderate to severe pain requiring opioid therapy for more than a few days.

OxyContin

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For around-the-clock pain: OxyContin™Cli

10 mg q12h

If a nonopioid analgesic is being taken, it may be continued.

Warning: Respiratory depression occurs most frequently in elderly, debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. See WARNINGS and PRECAUTIONS Sections in professional prescribing information.

For supplemental analgesia: Immediate-Release (IR) Oxycodone

5 mg administered 1 hour before anticipated incident pain 5 mg administered for breakthrous

5 mg administered for breakthrough pain (if needed)

Note: If more than two rescue doses are needed per day, OxyContin should be titrated upward.

Converting to OxyContin.

Fixed-Combination	Opioid/	A
Nonopioid Products	_	OxyContin

Dose of regular-strength products (eg, Percocet*, Percodan*, Tylox*, Vicodin*, Lortab*, Lorcet*, or Tylenol* with Codeine)	Recommended OxyContin conversion dose range	IR oxycodone rescue dose for breakthrough pain*
1-5 Tablets/Capsules/ Caplets per day	10-20 mg q12h	5 mg
6-9 Tablets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg
10-12 Tablets/Capsules/ Caplets per day	30-40 mg q12h	10 mg

Note: The nonopioid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opioids when initiating OxyContin therapy.

^{*}See professional prescribing information for immediate-release oxycodone.

EASY TO DOSE.

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyContin Titration Guide

	OxyContin Tablets q12h dose	IR oxycodone dose for rescue	
	10 mg q12h	5 mg	
0	20 mg q12h	5 mg	
10mg	30 mg q12h	10 mg	Titrate the OxyContin
0	40 mg q12h	10 mg	dose if more than two rescue doses per
20 mg	60 mg of 2 h	26 15 mg =	day are needed.
0	80 mg q12h	20 mg	
40 mg	120 mg q12h	30 mg	
	Continue titrating, if ne	cessary, using the TeleMeE prin	ciples below.

Titrate patients every 1-2 days, if necessary.

Increase the dose by 25%-50%, if necessary[†]; do not increase the dosing frequency.

Manage breakthrough pain with IR oxycodone" at 1/4 to 1/3 of the 12-hour OxyContin dose.

Elevate the OxyContin dose if more than two rescue doses are required per day.

[†]For patients taking OxyContin 10 mg q12h...

- The next titration step should be 20 mg q12h
- Breakthrough pain should be managed with IR oxycodone 5 mg



Please see accompanying professional prescribing information.



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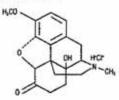
Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 83 of 110. PageID #: 400557

OxyContin™ 10 mg Tablets OxyContin™ 20 mg Tablets OxyContin™ 40 mg Tablets (Oxycodone Hydrochloride Controlled-Release)



WARNING: May Be Habit Forming

nesociation (in the procession in physicial season controlled -release) statistics are an opoid analogatic assigned in 10 arg., 20 mg, and 40 mg tablet strengths for drail administration. The tablet strengths describe the amount of only obtained per tablet at the light collection of said. The structural brings of the opposition of a strengths of the opposition of participation or a tableties.



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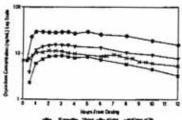
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potants.
PHARMACOTMETICS AND METABOLISMS
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Absorption About 50% to \$2% of an one dose of composions maches the central comparisment in parties in a parentrarial dose. This high out becomestable is due to the one-optioning the open analysis. In some investments the 1% of absorption is 0.4 flows to inside release and conjections. In contrast, Depthorin takens entails a options absorption release and conjections. In contrast, Depthorin takens entails a options absorption patie. The apparent supportion half-direct of 0.6 and 6.5 hours, which describes the initial of organization than the balant belowed by a propaged misses.

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20 mg OnyCortin	207.5 (26.9)	21.4 (36.6)	32 (57.8)	11
40 mg ChyCortin	423.1 (33.3)	393 (341)	3.1 97.4	44
Multiple Derge 10 mg ChyCartin Tubles gilith	123.6 (28.4)	15.1 (21.0)	32 (99.5)	72 (48 1)
5 ng immediate- mkase gSR	993 (96.2)	15.5 (28.4)	15197	7.4589
tior single-cose AUC =	AT, traduct	SERIC-RE.		-

Food Effects in contract to immediate-release formulations, food has no significant effect on the absor-tion of approxima trace Deployers. Depositions measure from Deployers have s per independent.

Commissions (Continued and Continued and Con

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rule subjects have, on average, pleases onycodore concentrations up to 25% higher than les on a sody weight adjusted batis. The reason for this difference is unknown.

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CLINICAL TRALE.

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ing our day. The average botal daily does was approximately 105 mg (per day. Soldes in Nicholater) Alexandrous Alexandrous, parallel group story was conducted in 133 patients. A double-blant, placebo-corrected, feed-does, parallel group story was conducted in 133 patients with moderate to be every autocontrolling pairs, who was judged as burning subsequest pairs double conjusting of the invariant non-standal area-informatory temps, in the story, 20 mg Conjusting of the invariant non-standal area information parallel in mode and story and with a minimum effective plasma on opcodence concentration of approximatily 5–10 agreed, in a double-blant, active-controlled, consistent study involving 37 patients with two-back pairs with a minimum or provided with green opcodes are doubled burning. Opcoders administration (17th provided integrated specialism of the intertwitin estimation of approximation of the provided integrated specialism.)

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A single-dose, double-bland, placebor controlled, post-committee study of 162 patients was conducted statisting posted doses or DepCosten (19, 20 and 30 mg). Thereby are 30 mg of DepCosten pare sealwhafet posts analyses eithed compared to two expectations is mg Justines and to 15 mg Investigate release expectation, while the 10 mg doses of Confusions was intermediate between both the immensions existent and committee of the production and places and compared to the production of Confusions was intermediate between their the immensions existent within the other than the production of Confusions and intermediate between the production of the production of

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estiblishinis.

Other Clinical Blads
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actualistic from the according to be according to the a

For opticl-have patients, the inversage total daily does of CaryCortian was approximately 40 mg par day. There was no evidence of carycodopes and metapolitis accountation names a moretia of therapy for cases pain partiers the average total daily does with 100 mg leaves 20 to 700 mg) per day. There was a significant decision in scale policy-instited date with 20 mg leaves and the constitutions, while the first benefit select of the trays Development of significant blockers and participated was selected in the constitution.

RODATIONS AND USAGE
ON/COMMS** Library as a Commonwealth of the Commonwealth of Confederate Pythocotholese
Applicated for the management of moderate to stress pain where use of an application of adoption and page a appropriate for more than a law days. (See: CLARCAL PROJECT, CL

CONTRIBUTIONATIONS

Contribution in completed and in patients with linewin hypersensativity to copcodium, or in any situation when opinion are contributed and. This includes patients with significant individual situation when opinion are contributed and to the abstance of associative resistance) of associative resistance of associative patients with accordance association of the abstance of associative resistance of associative patients with accordance association of having paralysis issue.

WARRINGS
ONE of the "DISTRIBUTE ON THE CONTROL OF T

Train or A POTENTALLY TRACE DOSE OF CITICODORIE.

Reciphratory department the criter hazard from all opcord aponets preparations. Proprietory department must feel hazard from all opcord aponets preparations. Proprietory department must feel hazard from all opcords in socio-beleast patients, or when optods are given in comparation with other particular disposals and control production with other particular disposals are promoted.

Convictions tolerate the used with extreme caution in patients with significant chronic obstactive positronary disease or cor parametrial, and in patients having a substantially connected pressure ment cause the operation in any patient of personal interest patients and position of patients in these patients alternates on overview analyses and social and operation all many patients are produced analyses alternate the overview analyses alternate through other patients.

In these patients alternative one-overview analyses alternative overview analyses alternative one-overview analyses alternative overview analyses alternative overview.

the improving large states and an advantage and extended interview and security. The inspiratory decreasant interiors of opixide include carbon disothe retiretion and secondary elevation of completes and pressure, and may be markedly exappleated in the presence of head rightly intercernial lesisters, or other sources of presenting internaceal presence. Oppositions produces effects on pupility response and consciousness which may obscure rescribute size of further recreased in resistantial protein in patients with near injuries.

obscure recording togets of Arther extracted in emiscating potation in patients with head righted. Physiolatinise (Effort) — the analyses of the properties and the properties of the analyse of the ana

PRECAUTIONS

PRECAUTIONS
Covering (projections hydrochtenia committed-visitate) tobiets are intended for use in patients who inspect out past therapy with as operate aprovate of more than a live days dept-point. As with any operate approach as operated approach of more than a live days dept-point. As with any operated approach to obeing registers industrially operated approach to obeing registers industrially operated approach to obeing registers industrially operated by the same principles that apply to the use of satisfar controlled-visituates could unappear to the INCOCHTONS along that apply to the use of satisfar controlled-visituates could unappear to the INCOCHTONS apply to the use of satisfar controlled-visituates and extended here a fair of integritation and pasted in cases when the benefits of operate satisfars controlled with other drugs, and include the represent cases when the benefits of operate satisfars controlled with other drugs, and include the represents cases on the benefits of operate satisfars operated the foreign registers of the cases of the operated of the controlled visits of the operated of the part of the case of the part of the part of the case of the case of the part of the part of the case of the case of the part of the part of the case of

total exactions with respect or surprise of legals, publishary to resist fundamentally interesting of control of the control o

this will collect symptom. And which the properties of the properties and great or for the management of pain in the immediate post-operative period (the first 12 to 24 hours belowing surgery) for pain in the immediate post-operative period (the first 12 to 24 hours belowing somethy) for passents not previously being the drug, because its safety in this period has not previously being the drug, because its safety in this period has not been properties.

Privide who are shapfy working Op/Cortin Lablets as part of ongoing analysis; benoy may be safely continued on the strug it appropriate desage adjustments are made consisting the providence, other drougs plean and the temporary changes in physiology caused by the surju-cal leave-entire (see PHECALTICKS: Cring-Oring Interactions, and OUSAGE AND JURINIS-cal leave-entire (see PHECALTICKS: Cring-Oring Interactions, and OUSAGE AND JURINIS-

TPATION).

One in Francisch Stillary Stock Disease
Opposition was graam of the application of Odd and should be used with caution in satients
with bilary text Seases, excluding scale samonastile. Opioche like topcodone may cause increase
is the seatm partylese level.
Following and Physicial Departments
Teachings are seed for increasing dozens of opioche to maintain a selfered affect such as ame-gically in the diseases of observations after south diseases. If Physical department
is the occurrence of withdrawed specification after south decorative and a study or you dema-listation of Jan antiagonate, Physical dependence and tolerance are not unusual during chronic opiosities.

getti iji in the disserce of ordinate propriessor or their all proposed a size or upon admin-tion occurrence of withdrawal springers after all propriess and interactic all a size or upon admin-tration of as entapoleti. Physical dependence and streamer are sold useful aftering cross opposite thereby.

Significant behinds should not occur in most of the potentia treated with the lowest desire operations. It should be expected, lowering that a fraction of carrier patients will device on ordinate depth of the control of the con

medication.

Patients should be advesed not to adjust the since of OnyConton without consulting the pre-scribing portessional.

Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 84 of 110. PageID #: 400558

- Patients should be advised that ChyContin may impair mental and/or physical ability require for the performance of polantially hazandous tasks (in g., criving, operating heavy machine

- for the persumance or positively make the second of the control nervous system dependances (asked not combine boyContie with altohol or other central nervous system dependances (asked not control nervous system dependances) because additions effects may occur. In the other of the proposition of witness of the other or positions and the other of the other of the other of the other of the other other
- was precinited.

 8. Patients should be advised that they may pass empty matrix "goods" (tablets) via colosion or or in the stool, and that this is of no concern since the active medicatios has already been apported.
- Thy or in the salon, so we want to be a selected from the selected and selected and selected from the selected from the

Liberatory Monitoring of pleases concentrations seen in clinical populations, the varying degrees 0 still not broad range of pleases concentrations seen in clinical populations, the varying degrees of sain, and the development is Passing options on oppositions of the active ship substance may be of visite in street installation of complex capes.

Attractions with Alcohol and Engs of Abuse
Disposons may be expected to have additive effects when used in conjunction with alcohol,
office opicies or alick drugs which cause central nervous system depression.

Use in Diagrap and Accord Additions

Deployers in an opposit with no approved use in the management of additive chordent. Its proper is usage in uservisate with noisy or accorded dependence, either active or in remission, is for the management of pain requiring opicid analysis.

the management of pain requiring opinious arrangement of pain requiring the Dury-Disty Internations. Opinious arrangements, including DepCoales, may enhance the neuroniuscolar blocking action of seasibilit muscle arbitraries and produce as increased degree of respiciously depression. Opposition is institutional in paint to opportphone via CPP2DS. While this pathway may be blocked by a variety of dings in e.g., certain cardivaceasat into and autoripressions), such blockeds has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible electron, however.

to aware of the possible interaction, however.

Use with CAS Depressants
DryCortic, the all open of malgedics, should be started at "- to "-, of the usual docage in patients
who are concurrently recovering other central nemous system depressants including soldatives
of hypococs, general amentiveits, plenatheuries, centrally acting anti-emistic, transpulsant
and stoches because respiratory depression, hypothesion and system depression remains, transpulsant
result. No specific interaction between torycothne and management decides withboars has been
observed, but caution in the use of any opioid in parients taking this cities of drugs is appropriate.

Autography
Studies of population in animals to evaluate its carbinopesic and mutogenic potential have not been conducted owing to the langth of clinical experience with the drug substance.

beer conflucted owing to the length of clinical experience with the drug substance. Preparating Transcenic Effects — Category 8: Reproduction studies have been performed in crits and cal-bits by our administration at obese up to 8 major (48 major) and 125 major (1375 majorn), majorchine); Transc doses are 4 and 60 lance a human dose of 120 majora (1375 majorn), majorchine); Transc doses are 4 and 60 lance a human dose based upon majorini; The results of not marked evidence of farm to the fature of the onycoders. These are, noverence on administration of during and well-controlled studies in preparant women. Secures animal reproduction studies are sof always predictive of human emported, this drug about the seed during pregnancy only if clearly needed.

Norterappend Effects — Recruits whose mothers have been taking opposition districts whose mothers have been taking opposition districts with another reporting depression and/or withdraws symptome, either at 54th and/or is the nortality.

hurtery. Labor and Delivery. On/Curtis is not encommended for size in women during and immediately prior to labor and delivery accusate critic objects may cause regulatory depression in this erestorm. Muscling informations of exproduce have been detected in treast. With traveral symptoms can occur in breast-flavfled gridam when maternal administration of an opicide strategic is stopped. Ordinarly, number should not be undertained while a patient is receiving OnyCordin since onycodote may be excrited in the milk.

since engagedate may on experience our registers below the age of 18 have not been established. Salety and effectivement in positions, below the age of 18 have not been established with the disapped from of expectation. However, coycodone has been used extensively in the policiatic population in other disapp forms, as have the enclairest used in this formulation, lost possible increased risks is executed from the use of this from conjugation by expectating positions of extension policies and other disapped and policial for the use of the positions weight positions of extensions and policial for the positions of the conjugation of extensions and policial for the positions weight (see OCSAGE AND ACMARSEATACION). It must be reinnest level that DayConfix tablets cannot be crusted as dividant for administration.

or divides for administration.

Contrate that

In contrated pharmacockinetic studies in elderly subjects (greater than 65 years) the clearance
in contrated pharmacockinetic studies in elderly subjects (greater than 65 years) the clearance
of conjections appeared to be subjetly estudied. Compassed to young elderly, the planta concelestations of prorpodule were accessed approximation (75 in ordinate that with appropriate inspotency and the custom decision of personal participations and the custom decisions and delete plantance are appropriate for the greater
patient. As with all opinions, the stanting done should be educed to "to b" to the original patient.

As with all opinions, the stanting done should be educed to "to b" to the original patient.

According impairment

A sould of One Continue patients with hepatic impairment indicates greater plantas concentrations
than struct with normal function. The initiation of therapy at "to b", the usual dones and careful does that one is warranted.

Decay impairment

for one transce is warrante.

April (majorite) with renal impairment, as endersed by decreased creativine citariance (<-00 mil.min.), the concentrations of outprotone in the plants are approximately 50% higher than its subjects with domainmal function. Does initiation should follow a conservable approach. Ocsapes should be adjusted according to the clinical relusation.

ADVERSE REACTIONS

ADVERSE REACTIONS
Serious servines nearbons which may be associated with Ony-Contin "(prycodone hydrochhode controlled-neasas) table! therapy in clinical use are those observed with other opioid analysis, such participation, such participation, and the properties of the properties

incusin serious automatic is many of these events during instation of therapy may be minimized is many cases the frequency of these events during instation of the avoidance of targe even in the plasma concentrations of the oppole. Many of these advente events will called decrease in laterably as DayConth therapy is continued and some digner of therapes of the decrease in laterably as DayConth therapy is continued and some degree of the lateral is de-

in canical trials comparing On/Contin with immediate-release exposions and placetor, the most common adverse events (> 5%) reported by patients (pts) at least once during therapy wants.

Die 1	OnyCor e=22 # pts (7	Ri n-	4535 -225 41 (N)	,	acebe = 45 pts (%)	
Constitution National National Sommittee Sommittee Sommittee Property Verning Headsche Dry Mouth Actheria Swesting	52 52 52 29 29 27 17 13 13	(23) (23) (13) (13) (13) (14) (15) (15) (15) (15) (15) (15) (15) (15	58 60 55 35 28 21 19 15 15	部のでは、	3 5 2 4 1 3 3 1 1	C) 2000000000000000000000000000000000000	

The following advises appellences were moorted in CryContin treated patients with an incidence between 1% and 5%. In depositeding order of requency they were amorted, revocates, resources, resources

sea and worntung, stomatitis

Nationic and Lymphatic Implicationopathry

Nethologic and Comphatic Implicationopathry

Nethologic and Comphatic Implications, edema, perighteral sidema, thirst

Nativous: abnormal gast, agustion, amnesal, opperansalization, depression, emotional lability,

staticination, hippophressal, hypothessal, aphostoma, makises, paresthesia, speech doorstet stapor, timities, transce verigo, withdrawal syndrome

Respiratory, cough moressale, hyparryptics, voice alteration

Skirt dry skirt, acticitative domination

Special Senses amorestal verient, table pervention

Urogenetal dysuita, bernaturia, impotence, polyptila, uninary releation, urmation impaired

Urogenetal dysuita, bernaturia, impotence, polyptila, uninary releation, urmation impaired

Orogenistic dysuria, hematuria, impotence, polyedia, unnary relation, unrusten impaired DRUG ABDSE AND DEPENDENC (Addiction)

OxyContin** is a mu-agonist opioid with an abuse liability similar to morphine and is a Scredule is controlled betalance. Oxycootone products are currinon targets for both drug abuses and drug addicted, Selectaire. Oxycootone products are currinon targets for both drug abuses and drug addiction (origing dependence, psychological dependence) is characterized by a procoupulation with the procurement, founding, and abuse of drugs for non-medicinal proposes. Drug depen-dence is tractable, utilizing a multi-decicious persoach, but relating se occurring integration and decided to opioids legislantarily used in the managament of pain is very rise. "Orig seek-rable beginness to very common in addicts. Telenocupation with achieving adequate pain relation and so appropriation behavior in a patient with poor pain control. Macchinely adequate pain relation the patients and propriation of the patient seek propriation of the day and dose-limit-ing side affects.

Plepticums adole be aware that psychological dependence area very limited.

In global shocks be aware that psychological dependence may not be accompanied by con-content towards and symptoms of physical dependence in all addicts. In addition, about of spoids can occur in the absence of the psychological dependence and in characteristic by missele for no-medical purposes, other is commerciate with other specification substances. Cryboris consists of a cuspoplem rath, intended for onal use only. Pareferal version specification substances. In ord the tablet constituents, especially fallor, can be expected to result in local issue records and pulmonery granulomas.

OVERDOSAGE

OVERDOBAGES
Acute overdosage with respondence can be manifested by respiratory depression, souncelence propersional to stuper or correal, selected investe flaccodity, cold and claimmy disk, constricted pupils, bradycards, hypoteration, and clasts.

In the treatment of depotedence restributes, permany alterition should be given to the on-establishment of a patent sinvey and restributes of assessed or controlled vertication. Supportive restricts finishment of a patent sinvey and restributes of assessed or controlled vertication. Supportive restricts from a patent sinvey and restributes of assessed or controlled vertication. Curdiac aimset or artifactures in the patent sinvey and company and or deformation of account of controlled vertication. The pure opioid antapositists are indicated. Curdiac aimset or artifacture of celecular significant inspiratory or controlled in should not be administered in the absence of claimsets significant inspiratory or controlled on the depote of controlled to the physical depote antaposition of the administered curdication of the controlled on the physical depotence of the controlled on the physical depotence of the controlled on the physical depotence or co

DOBAGE AND ADMINISTRATION

DOYCOME "(IMPOSEME HYDROCHARIDE CONTRIBUT-MINIOR) TAILETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED, TAKING BROKEN, CHEWED OR CRUSHED, TAKING BROKEN, CHEWED OR CRUSHED DROCKSHIN THAT ITS COULD LEED TO THE BAPTO TRELEASE AND ASSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODOME.

TION OF A POTENTIALLY TOXIC DOSE OF DIXTODONIC. In tradicip pain it is visit to assess the placetim requirity and systematically. Thereby shoeld also be equivally reviewed and adjusted based upon the placets own reports of pain and side effects and the health professional's clinical judgment.

CAPCILOTE is introduced for the management of moderate to severe pain in putients who require transported for moderate to severe pain in putients who require transported every 15 med caps. The composite-release nature of the Cartillation alseved is to be electricisty administrated every 15 mans, Sec CLINICAL, PAVA-MACCIOES, PAVAMACCIOES, PAVAMACCIOE

may benefit inon asymmetric gothenics code greats in his investion to home, assente to home pain pattern, its unassity appropriate to treat a patent with only one optical for anound-the-clock thanky.

Intelligence of Therapy

It is concern to institute the design regimen for each gothert inchridusally taking into account the patient's prore opened anniques to submert. Altertion should be given to:

(1) the general condition and medical status of the patient
(2) the daily dose, potency and blad of the analyses/cipi the patient has been taking
(3) the misbelity of the convenion estimate used to calculate the dose of oxycodone
(4) the patients opicid exposure and opicid televance (if any).

(3) the statuted between pair control and advente expressions.

Care statuted be blain to use low whose doses of Oxycodon in patients who are not attractly opicid televant, as opicidity and the statute of the convenions of the control and advente expressions.

Care statute the statute the second of the advente expressions of the statute of th

Onycordin.

3. Round own to a dose which is appropriate for the tablet strengths unerstable (10, 20, and 40 mg tablets).

4. Decortinue at other amusi-the-clock optical dwgs when ChyCordin Therspy is initiated.

4. Decortinue at other amusi-the-clock optical dwgs when ChyCordin Therspy is initiated.

4. Decortinue at other amusi-the-clock optical dwgs when ChyCordin Therspy is initiated.

4. Decortinue at other amusi-the-clock optical dwgs when the specially patients incering the special optical dwgs and the special patients are stating point, and close optical deciration and inequant titusion are indicated until patients are stating on the new therspy.

Table 3

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral

(Mg/Clay Prior Opicid x Factor = Mg/Clay Oral Oxycodol Oral Prior Opicid Parenteral Prior Coloid Chrycodone Codeine Festacyl TTS Hydrocodone SEE BELOW SEE BELOW 0.9 Hydromorphone 20 75 01 15 05 Levorphanol Meperidine Methadone 15

Morphine 0.5 3 "To be used only for convention to and asycodome. For patients receiving high-dose parentenal opioids, a moint dottermative conversion to warranted. For example, for high-dose parentenal morphine, use 1.5 instance of 3 as a multiplication factor.

It is all cases, supelimental assigness (the between should be made asystible in the form of immediate-release onal onycosome or another sustable short-acting analyses.

TIONS). Convenion from Plandermal Fertiley to Day-Confer Epitien hours following the empraid of the transfermal fentanyl patch, Oxy-Conffit heatment be included. Although their holes no systematic assessment of such convenion, a con-servative oxy-codious does, approximately 10 mg of the of Day-Confer, should be initially sub-stituted for each 50 applit hetungly transfermal patch. The patient should be listened to locate the day terrain as there is very limited crinical experience with this conversion.

Is for early fittation as there is very limited clinical experience with this coherension. Managing Espectral Opisid Adversal Esperiences. Most patients receiving coloids, especially those who are opisid rather, will experience side effects. Trequently the side effects from Chys Cortin are transless, but may incurs evaluation and management. Adverse events such as consisponts should be articipated and therets agreessed y and prophyractically with a stimulater boother analysis stool sediesser. Parients do not susually become to became to the consistency effects of opisids. Cheer oppoid-related sed without such as sediation and assesse are insulty self-limited and chief on the propriet and should be consistent with anti-emetics or other modisities may relieve these symptoms and should be con-idered.

Pollents moselving DayContin may pass an intact matrix "shoet" in the stool or via colosta. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Polletis incideling Despotation may pass an intext mater. Tyrow in the second or via consumptions gives contain title or in residual depreciation and as of no clinical construction. Advisinguilization of Disages. Once therapy is incided, pass place and other opioid effects should be linearisely essessed. Palents should be integrated to advisate effect (generally mid or no pain with the registration of one of the behalf of advisate effect (generally mid or no pain with the registration and or no more than their observables). Because stately-state plasma concentrations are approximated within 24 to 35 hours, dissipation and within 24 to 35 hours, dissipation and an area document to the approximation of the contraction of the second state of the contraction of the c

the standard or a search agreements (seed acresses events are under control, upward stroform should controlle their old pain costrol.

During partods of charging analysise cequimiterities, clickulting initial thration, frequent conflact
is incommenced between physician, other members of the health-care learn, the publish and
the carecylarithrania.

Supplemental Analysisia
Most causer patients glean around-the-clock therapy with controlled-whase opioids will need
to have immediate-release expectation available for "restour" from breakthrough pain or to prewest pain that docum predictably during controlled patient accentrate (includes plan). Rescue medication and be immediate release expectation produces, amen alone of it comments analypeace should be precibiled at in its for the 12-hour Confloration doce as shown in Table 4. The
rescue medication is doded as meeded for breakthrough pain and acressioned deformation and confloration and the doces of rescue medication as enabled with
the medication is doded as meeded for better depends and acressionation are needed withthe rescue analysis in comments and the doces of rescue medication as enabled with
an excess analysis in comments of the physician massing the patient's analysis is per left of the patients.

DayContin g12h Dose (mg)	pm Fescue Oose kmmediate-raleus oxydodone (mg)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×20 mg)	15
80 (2×40 mg)	20
120 (3×40 mg)	33
Maintenance of Therapy	

Adarterance of Therapy. The intensity of the translation of the particular and particular analysis will maintain adequate analysis with acceptable side affects for all timp as pain retire for increasing. Should pain enter the fine does are be immunitarily increased to m-establish pass control. The method of therapy adjustment outlined above should be employed to m-establish pain control. Outlined above should be employed to m-establish pain control. Outlined should be immunitarily increased to the continued need for around-the control that pay should be membered periodicity (i.e., every 6 to 12 monthly as approached only all pays the pays of the control that pays all pays the membered periodicity (i.e., every 6 to 12 monthly as approached point the major and the pays and the

polisis.

Constation of Therapy
When the gatient on larger mouses therapy with DeyContin tablets, patients incohing doses
120–60 mg/day can essailly have the therapy stopped alterptly without incident, incovered, higher doses should be topined over several deys to prevent larger and symptoms of withdraws in the physically dependent patient. The day's dose should be recipited by approximately 50% for the first here days and then midically by 5% every two days thereafter until the total dose machine the dose moortmended for opcid naive padents (10 or 20 mg q17s). Therapy of the hard has discontinued.

for the first two days and then induced by 25% every two days thereathe until the focal does nucches the does recommended for opcid salve palests (10 or 20 mg q17%). Therapy can then be deconfined, it is salve the property should be stopped. The done should be slightly increased until the signs and symptoms of opcid withdrawal disappear Tapwing should then begin again but with principle palests of time between such dose netection. Conversion them OrgCodia to Paresterar Opcide to Some between the dose not exist. In this treatment with about 50% of the estimated explainations of only dose of parenthral opcid deviced into suitable individual doses besed on the appropriate dosing esternal, and shoto based upon the potent's control of the estimated explainations of the significance of the sign

SAFFTY AND HANGLING

Chyclonian¹¹ (procedone hydrochloride controlled-release) takiets are solid dosage forms that pose no longwer health risk to health-care providers beyond that of any controlled substance As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

HOW SUPPLIED

HOW SUPPLES

(Exploration Exploration bydrochishide controlled-release) 10 mg tablets are round, unscorred, white-colored, convex tablets bearing the symbol OC on one side and 70 on the other. They are supplied as bidden, and the other threy are supplied as bidden, and the other threy are supplied as bidden, and the other threy are supplied as bidden bydrochishide controlled-initiation) 20 mg tablets are mund, unecond, girth-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as biddens.

AND 59011-190-10: creat-resistant closure, opeque plastic bottles or 100 CopCoREs (opequed the hydrochoide controlled reliases) 20 mg babbet are shund, under pell-colored, comercialletts bearing the symbol OC on one side and 20 on the other are suppled as follows:

NBC 59011-100-10: child-resistant closure, opeque plastic bottles of 100 CopCoREs (opequed to hydrochoide controlled reliases) 40 mg abbits are round, under yellow-cocored, control tablets bearing the symbol OC on one side and 40 on the other are succided as follows:

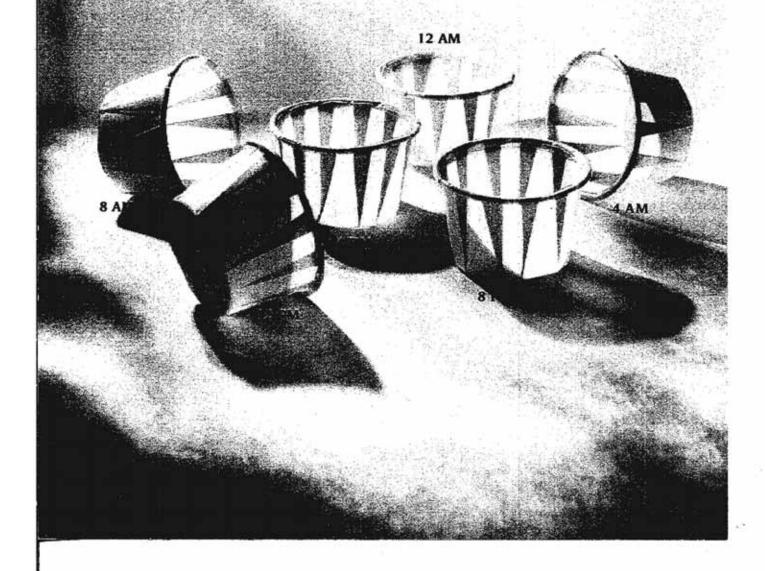
yellow-colored, convex tablets bearing are symmetric as supplied as follows:
are supplied as follows:
ARC 55011-160-100 chief-resistant closure, opaque plastic bottles of 100
Store tablets at corrosaed recom temperature 15–30°C (59–86°F).
Dispense in tight, light-resistant containes.

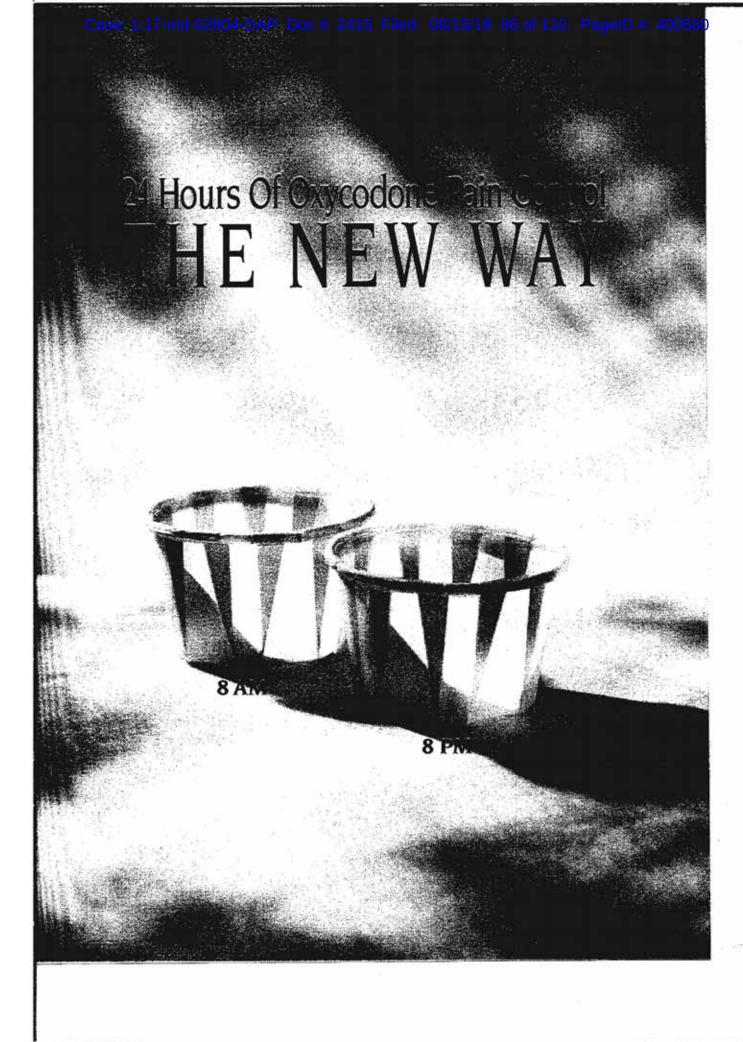
Cabinder Form Required.
Federal law probbits dispending without preceiption.
Manufactured by The PF Laboratories, Inc.
Totows, N.J. 07512 Distributed by Purdue Pharma L.P. Norwalk, CT 06859-3590

CopyrightiD 1995, Purcue Pharma L.P. U.S. Patest Numbers 4,861,598: 4,970,075; and 5,266,831

December 5, 1995

24 Hours Of Oxycodone Pain Control THE OLD WAY





INTRODUCING



10mg

20 ag

40 mg

The first and only q12h oxycodone.

Brought to you by the makers of MS Contin® Tablets CII (morphine sulfate controlled-release).

Heavy promotional support planned.

- Promoted by over 300 dedicated professionals—the same sales force that boosted sales of MS Contin* to over \$100 million.*
- Journal advertising and direct mail to doctors, nurses, pharmacists, hospitals, hospices, and managed care organizations.

Wholesaler/Chain Introductory Offer

Extended Dating: 60 days' extended dating* (total 90 days)

Promotional Period: January 1,1996-March 29,1996

First Ship Date: January 2, 1996

Retailers can earn a stocking rebate directly from Purdue Pharma based on their initial order of OxyContin purchased from January 1,1996 to March 29,1996.

Order your initial supply of OxyContin Tablets now! Orders must be accompanied by a DEA 222-C form; no phone orders accepted.

*Please submit your order on a separate DEA 222-C form to receive extended dating.

^{*12-}month sales through October 1995. IMS Drug Store and Hospital Audit, October 1995.

Promotional Ad Slick

Now Available Through



The first and only q12h oxycodone.

Brought to you by the makers of MS Contin® Tablets CII (morphine sulfate controlled-release).

Pharmacy Introductory Offer

Receive a stocking rebate on your initial order of OxyContin Tablets purchased during the introductory period: January 1, 1996 to March 29, 1996.

Complete coupon, enclose wholesaler invoice as proof of purchase, and receive rebate directly from Purdue Pharma L.P.

Don't delay! Order your initial supply of OxyContin Tablets today.

Retailers can earn a s	anuary 1,1996 to March 29,19 tocking rebate on their initia e HCl controlled-release).	
Store Name		Date
Address		
	State	ZIP
City		

To receive your rebate, submit a copy of the wholesaler invoice showing your purchase of OxyContin Tablets during the introductory period (January 1,1996 to March 29,1996). Mail to Purdue Rebate Offer, P.O. Box 81771, Chicago, IL 60681-0771. This form must be sent with wholesaler invoice. No forms accepted after May 1, 1996. Please allow 4 to 6 weeks for delivery of your check.

MS Contin is a registered trademark of The Purdue Frederick Company.

Promotional Ad Slick

INTRODUCING





Small, color-coded tablets (actual size)

Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Item #
10mg 100's bottle	59011-100-10	\$107.16	\$2.00	
20mg 100's bottle	59011-103-10	\$205.10	\$4.00	
40mg 100's bottle	59011-105-10	\$363.91	\$6.00	

^{*}Earn an additional \$3 rebate for stocking two or more different strengths of OxyContin. Maximum rebate allowed is \$15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. No phone orders accepted.

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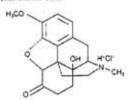
OxyContin™ 10 mg Tablets OxyContin™ 20 mg Tablets OxyContin™ 40 mg Tablets (Dxycodone Hydrochionoe Controlled-Ricease)



WARNING: May Be Habit Forming

SEADORIPTION

On Contin 1 Supposition by processing or provided relates tablets are an oxided an open only
specific to 10 mg. 20 mg, and 40 mg states steengths for drail administration. The states desingly
obsorber the amount of drail-ordering our self-state in years channels state. The structural forms
is for drail-ordering reproductions as a 10 flower.



Chilb-MO. HOL

MW 351 83

The chamical formula is 4, 5-spory-14-hydroxy-3-methoxy-17-methyltroscharus-6-one

hydrocterode Organization is a write, counters crystalling powder derived from the opsium alkabot, installing Consideries hydrochlodied deceives in water (1 g in 6 to 7 mil.). It is skiptly optable in alko-ter all optation is alken partition certification (1 J.). The alkents contain the bildware, section in production is alkents of the contained of the production of the contained bildware, section, inappression of the contained discounter that alkents of the contained of

CLINICAL PHARMACOLOGY

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assects effects of devications misself analysists, expected and telenge or missector. Let all pure object apposits, there is no calling offects or amples, such as in seen with period nists or non-deploid analysists.

The period mentalment of the analysists action is unknown. However, specific CNS optical recog-tors for endogenous compounds with populative has been identified throughout the bear and grant occur and play a rise in the analysis effects of this discretified throughout the bear and grant occur and play a rise in the analysis effects of the interpolation Chycopone groduces respiratory depression by direct action or brain stem respiratory calls. The respiratory of consistor includes both a responsable in the responsable effects of the brain stem respiratory centers to increases in carbon disable tension and to electrical plannation. Som interpretory cereans a province in real-conditions entered and or design and Composition Compresses the cough infere by direct effect on the cough cerear at the modula. Anthonis effects may occur with dops over than frost unusing required or adaptive. One occur assess missis, even in tradit carbonal. Proport quality save a sign of could over-dose but are not carbonal condition. Marked mycrobials rather that: missis may be seen due to hyposal to creditor shallation.

hypoda in overdose situations. Controllectural Real and Other Smooth Missolic Christopher quasies, a reduction in mostler pasculated with an increase in introduction in the startum of the stormum and cusoterum. Depetion of food in the small least-time is critique also propolated contractions are devisated. Propulsing particular varies in the other are secretable, while store may be internated to the opetic of scalars in resting in contraction. Other cooks de-discussed effects may equide a reduction in genome, Using and provincials access some, speam of spincaries of Cooks and instructed sections in Section Missalization.

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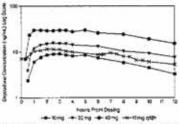
coment of followings.

Concentration—Adverse Experience Polariomatuse
Conjourner Solids are associated with fysical opicid-relates adverse experiences similar to
those seen with immediath-relates expressions and all opicids. Them is a govern institution of these more passing opicioters plants opericary than and inhamising from opicidity plants or coverythma and inhamising from opicidity plants or coverythma and inhamising from opicidity plants or coverythma of the investigation of opicidity or in opicidity opicidity or in opicidity of the overlate from the plants of opicidity on in opicid-discovery deposition of the overlate from the filtration of the opicidity of the overlate or opicidity of the overlate or opicidity of the opicidity of the opicidity opicidity of the opicidity opicidity.

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Appendix to STS of an oral cost of expositive maches the central concentrated in compartment in compartment appeared to 35 st of an oral cost of expositive maches the central cost of expositive maches and oral to a cost of expositive maches inscription and oral to the production of expositive maches inscription expositive maches and expositive maches

Planma Coycodone By Time



Cour proportionality has been established for the 10 mg, 20 mg and 40 mg table; strangths to both peak yearns concentrations (C_{max}) and extent of appropriate (AUC) (see Table 1 below). Given the short half-like of elimination of bry codons from DoyCortin, steady-state plasma con-

descriptions of exploadone are activised within 24-35 hours of instation of description between its asset, in a study composing 16 mg of DeyCordin every 12 boars to 5 mg of eministration on conditione every 6 boars to 5 mg of eministration was foliated to the properties for ACS and instationals was foliated to the properties of a Cordinated to ACS and activised to the properties of the condition of of the condi

Pagetter/ Design Form	AUC (rg+ht/rs2r	(س	fina enti	Tough Conc. (hghru)
Single Date 10 mg DeyCorde	1007 (25.6)	10.6 [301]	27(41)	A4
30 mg ticyCoron	307.5 [25.9]	21.4 [38.6]	3.2 (57.9)	4.1
40 mg Gry Contin	(23,1 (33.3)	36.3 [34.0]	3.1 (77.4)	8.8
Multiple Desit 16 mg DayContex Tupins of th	133 0 (38.19	15.1 (31.0)	12 (45)	7.2148.15
5 ng minedole- reliaux clift	99-0 (96-2)	15.5 (25.8)	1.6 (46.7)	7.4 [50.9]
ffor single-door AUC-	AUC. at multiple-o	DOM AUC - NUC.		

Food Effects in contrast to immediate-release furnications, tood has no significant effect on the absorp-tion of disproduce train DayContin, Daycodone release from DayContin tabless is gH Independent.

Distribution
- Strength on the Control of the Contr

Digitization and committee of exists from pair material enterior of the Missister of Missister of the State o

expressors

Opponing and its metabolites are exit. He opiningly us the kindly. The amounts recaused in the united have been reported at tell out; the expressions up to 1996, consequent opponing us to 1996, whe organized propositions us to 1996, whe organized propositions us to 1996, whe organized propositions is 1996, both their and consequent of new board have been found in 1994 united but not qualified. The total plasmit character was 0.8 Limit for exhibit.

Visign for August for amount.
Electry
The gratinal concentrations of psychologic limit only normality affected by age, being 15% grader
in 65647 as compared to young excitors. There were no differences in adventile event record-ing between young and 65649 bubbless.

Ingliberation young and accent you, eco. Gendar Female stakeds have, on vernice, plasma devicadore concentrations up to 25% higher than make on a body weight adjusted basis. The reason for this dilivence is unknown. Speak "makiment" Prejentary data than a study inhabiting patients with mild to severe make dystituction tone-trains characte. <50 millimit) show pells patients with mild to preven make dystituction tone-trains characte. <50 millimit) show pells patient anyocopous and nonzerodosis comprised make 55% and 55% sight integrationity and ALC visites for page-door, independent and cov-mentations 55%. 55% and 45% higher than normal subjects, inspectively. This is accommod by an increase is saddler but on by of the control in registratory also, constitution, or several other maks are so of ong effect. There was an increase in the of elimination for objections of only it hour (see PRSCA/TIONS).

exposions of only it hour use PSCARTONS).

Inspatio Impartment
Prelimmary calls bern a study invalving pulsars with mile to moderate hepatic dystunction
show pask plearing caycodons and instruyocolors occurrentations 50% and 20% higher,
respectively. This increase applicable, ACC values are 95% and 55% higher, respectively.
Organizations are accompanied by reconsists in some, but not other by 30% and 40%.
These differences are accompanied by reconsists in some, but not other days effects. The first instruction for deposition invested by 30 hours (see PRECARTORS).
Deposition is metabolised in part is 50°/20° to eyenophore which represents less than 15% of the total administration did not provide the present and the state of the state of

CLINICAL TRIALS

CUNICAL TRIALS

CopComin** "(expectation by spirochianniae controlled -reliaising) bibliets with existinged in totalist involving "13 perfects with either cancer or non-character pan. All parlients incisiving (by/Cortin wine direct given on the control of the project of the controlled in the controlled in the controlled in clinical stacked using pharmaconiants(e.g.) a postborous concentration. The encounter of these that indicated: (1) a postborous that controlled indicated object and distinct one-controlled controlled in the controlled indicated (1) as on the controlled in the controlled controlled indicated (1) as on the controlled indicated object and distinct one-controlled controlled indicated (1) and observed giase is to trough variation in plasma concentration and analysists, and (1) an observed giase is to trough variation in plasma concentration and analysists, and (1) an observed giase is to trough variation in plasma concentration and in stacked analysis (one-controlled controlled indicated operation of the same total district only drove. In the controlled indicated controlled in the controlled indicated operation of the same total district only drove. In the controlled indicated operation of the same total district only drove. In the controlled indicated operation of the same total district only drove in the controlled indicated operation of the controlled operation of the controlled indicated operation of the controlled of the controlled of the same with district of the controlled of the controlled

class-resizes corprocess at opposition state days detect, when present our or project rests of the company days of the company

Softer Chinese thats in color paper makely 200 patients with cancelvaluated and non-cancer in open-sized trials strucking approximately 200 patients with cancelvaluated and non-cancer pair, consel excellently to the sessions inner mechanisations, appropriate analysis effectiveness was make without regard to age, pendor, race, or disease state. There were no subsect thruly programme contented in patients including a wide range of medications common in these populations.

For coloid-halve petients, the workings total dusty case of DayContin was approximately 40 ms or day. There was no evidence of disyclotion and metabolits accumulation outline 5 months of thereap, for cases pan posteres the waveage total calls you was 100 mg bring 20 to 750 mg) and day. There was a spondered economic state position related and effects thereaf for consignation, during the first several weeks of demany. Development of significant telephone to the supplied with subtraction.

INDICATIONS AND USAGE

insprantors and dealer
(byContin)* tables are a controlled-referre oral formulation of drycosone hydrochloride
indicated for the management of moderate to severe park where say or opinio analysis is appropriate for more than a few days. (Sept CLINICAL PHARMACOLOGY, CLINICAL TRIALS).

appropriate for more than a level signs, so purchased a resemble control and a control

WASHINGS

DyCards: "Jurycockne hydrochloride controlled-relicion! TABLETS ANE TO BE SWALLOWED

WHICE, AND ARE NOT TO BE SHOUTS, DEVINED OF CHURCHD, TABLES SHORES, CHENTED

OF CREASED OPPOSEDS TABLES COULD LEAR IN THE APP

Percentagy prepression Percentagy arguments is this unief hazard from all optical agonist preparations. Perspection command of the percentage of the percentage of dealthand deferrit, usually indicating any en-tage offices in ordinary patients, or when optical using given in conjunction with other agency that depress registation.

that decides insciration. Conjunctions street do existed with extreme caution is patients with significant chronic costmu-tive partnershy disease or conjuntonale, and in patients having a substantially discretised res-placemy seative. Bypositio hypercaptive, or previously resource y deletistion in such selection, and usual translated droves of proposition and protested insciration drive to the point of series, in these patients adjustment protectional analyses about our consistency, and options should be employed only under careful moderal supervisions of the forest streets exist.

Mead Poury
The instruction of your essent effects of opioies include carbon closed entermion and secondary
The instruction of cerebrispied fluid present, and may be markedly enapprised in this prosent
of lead shung, intercesses lesions, or other sources of presidently included enterminated in present. Oxygodized produces deleted on pupiliery thorough and concounting enterorizonate country, or the time increases in miscratial pressure in patients with freed significa-

Concurred controllings larger at whither disclaims in meaninessing presents or parties in an in-minimal inference in Application for the city control in the control in the

PRECAUTIONS

General DryCortian ** (asyptodone hydrochloride controlled-risbasse) tablets are intended for uses in potentia who require only pain than by with an opicid agonal of more than a few days com-tion. As with any copicid analysis is its orbital to adjust the displayingment movedually for each papers (see OSGAL AND ASYMARTHANIDA).

point one of Oscilla And Andread Plant (1997) and the second of separate more causity of side platest dees OSCIAL AND Andread Plant (1997). Seeded of platests for treatment with Oscilla Control Seeded by several by the Service price of the service of the servic

popriodis.
The administration of asycodom, We all opcid analysiscs, may obscure the Seproidi of dis-load course in patients with acute abdominal conditions. Disposition may aggressive consul-sions in patients with controllers diseases, and all opcids may induce or aggressive consul-sions of selections.

et some terroid sittings.

Interactions and rother CNO Deprehenets

DopCornti, Neils depres analyses, smould be used with caudion and started in a related cosage
(*s to "not the secul discage in patients who are obscurredly receiving other cereal revious
system depression broading related between the process, press anothers, chandrage and
interactions are placed, interactive others musting in reportably openies on, typiciented,
producted selection of committing regard of these onigs are taken as pomishation with the stead
obsess of Ony-Cortin.

docts of DayCords.

Internations with Many dispositifications (Sound Analystics).

Internations with Many dispositifications (Sound Analystics).

Internations with Many dispositifications (Sound Analystics).

Application is present to present to the production of the production of the production of the Analystics of the Analystics of the Analystic of the Analys

Sized. Pattern who are strately ascelleng QuyCordn habits as part of ongoing analysis therapy may be safely continued on the drug if appropriate dosage ask, stimutes are made considering the procedure, other drugs given and the temporary changes in physically caused by the surposit intervention give PRECAUTIONS. Orug-Grug Interactions, and OUSAGE 4VO ADMINISTRATION.

Over a manifestronomy mate consists Chyclodron may cause speam of the springer of Cdd and should be used with causon in patients with bilary text Clanace, including acuse parcessitis. Opinids like onlycodone may cause increas-es in the senum arrylase lives.

Releases and Province Departmence Teleases is the react or increasing dones of booked to maintain a defined effect such as arrivable (in the subsect of deceads progression or other external factors; Physical decondence is the occurrence of withdraws symptoms after alrung decondence of the driving or open administration of an arringerest. Physical dependence and Solmanics are not unusual committee of the driving or open administration of an arringerest. Physical dependence and Solmanics are not unusual curring Solmanics.

Intradion of the arthogenetic Preparation dependence and softeness are not known drawing controlling gold thritisisy.

Significant before as should not occur in most of the geterots bested with the levest dozes of opticiones, it should be expected. Novelvor, that a fraction of cancer patients will develop a strategies of biotectics and require progressively large to obtain a fraction of cancer patients will develop a strategies of the strat

contact support (see DOSAGE AND ADMINISTRATION Certation of Thirtipy) information for Patients Chargerest it circuits y administration, patients increasing DoyContan (asycodone bydroctificide controlled-riblest) stated or their carridynam should be given the biblioming information by the physicial, mans, pharmacolour or carrying. It is present the property of the property of the physicial of the property of the physicial mans, pharmacolour or carrying the physician below were designed to only companies of the physician of

Problems smooth the advance to record eclander of breakthrough pain and adverse experiences counting during therapy, inclinducialization of dosage is essential to make optimal use of this modication.

resources.

3. Patients should be advised not to adjust the dose of On/Cordin without consulting the pre-sorbing portenional.

Case: 1:17-md-02804-DAP

4. Patents should be reced that Digital may major metal and or physical sorby required for the performance of coloribally nazarocals tasks (e.g., driving, operating heavy exacts—

for the performance or common CoyCostin with accord or other central network system (n)). Publish sinder one common CoyCostin with accord or other central network system concessants raised adds transcriberty publish by the orders of the prescribing physician, because additive effects may record. Attention of the according to the other, prepared should be advised so consult their physician requiring the effects of analysis and other at a publish and property on themselves and the effects of analysis and other and a serviced back CoyCords is a potential drug of about the through the property on themselves and the uniform short. They should overest a tom their, and it attends review be given to anyone other man the network of was prescribed.

Seen appoints. They show that a they have been receiving presented with Day Cortin for more than a few version and creatable of the top, is indicated, in they be appreciated to start the Decisions note, other than due hey decorations, due to the risk of perceivation of sand-sand symptoms. They show that the present of accomplishing producting additional insultion at the medication.

Laboratory Alboratoria).

Due to the forest energy of continuous concentrations where in difficult to build both. The visible progress of park, and this convidentment of park, and this convidentment of potentials, parama convision of measurements are usually and reconstruction of infection measurements. Playman convention for on the active of the parking both of visible o

indimensions with discinal and Dilugs of Abuse. Deyections may be impersed to have additive effects when upod in conjunction with stocker, other openits or vitor origin which cause control review system expression.

The arthrop and Approximations and the management of actions disorders, to perform or supported the country of the management of actions disorders, to perform usually in humanitaries with only or activate decreased in the management of the manage

the management of pain requiring opioid analysise. Qualification and produce the production of the management of the production of selected master releasable and product an increased degree of interleading objection of selected master releasable and product an increased degree of interleading objection of selected in masterial or part to controlled only of PP206. While this pathway may be solved by a variety of origin (a), certain conflict execution and anticopressants, such blockled that and the selection of the of circles appricance with this agent, Chromas should be selected that operations.

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Aturspeniony Studies of exp Studies of expenditure in animals to available to curdinaperic and mutageric potential have not been conducted owing to the length of dividual expensable with the drug substance.

bern conducted dening ihr ferhalf of circuit dependent with the drug substance. Profighatory - Entingent Effection — Contingent is Reproduction studies have been performed in rist and de-table by our administration at consists on all ringing (45 mg/m²) and 125 mg/mg (1475 mg/m²), impactives. That dozes and 4 and 60 times a framma occe based upon mg/m². The results do not regalt of a 544 addit (67 and 15 times the man occe based upon mg/m². The results do not require and what controlled photoes of projects of one occes. There are, incompress addition and what controlled photoes in projects of one follows the controlled photoes above and what controlled photoes in projects of one follows the controlled projects of in clearly medici.

mentary. Custor and Onlivery OwoCortin is not recommended for use in women during and interestubily prior to labor and delivery because oral options may cause resolvatory depression in the newdom. Alternal Section.

tyrang atemory, one concentrations of executions have been detected in brass) mile. Witnesself symptoms one concentrations of execution private when maternal administration of an opioc analysistic is supposed. Ordinally, surings through one be undertaken while a petient is receiving DayCostin since onycontain may be exceeded in the mile.

State symposium and the control of t

as divided for determinations. Ceptable Date in contraction associated in diseasy subjects (greater than 65 years) the classrance in contract of partner appeared to be startly reduced. Compared to year guide, the plasma concentration of concoders were increased approximately 15%, in clinical traits with appropriate violation of concoders were increased approximately 15%, in clinical traits with approximate violation of concoders were increased approximately 15%, in clinical traits with approximate violation (violation) and of the contract of the private parents of significant significant parents are approximate for the options of contraction of the contraction of contraction of contractions of contraction of contractions of

Record impairment:
A stay of Displacer in pulsors with highest impairment indicates grader places concentrations
for more with comas function. The industrial of the richy at 15 to 15 the usual coses and caretyl dose trader is viginanted.

A dissolvation is warranted.

Among trapismost in the second of the contracted consistency character (< 40 millions) and the second of the consistency of the contracted consistency (< 40 millions). The connectionation of insections in the plasma are approximately 50% higher transitions, with normal resolvation. Done interact should be low a conservative approach. Dones should be a significant execution to the clinical shutsion.

Gender Adherence in productionate tensions demonstrate up to 20% higher exerage plasma concentrations and genter frequency of topical opical advente exercis frequency of the magnitude of the magnitude of the adequated to the contract of the magnitude of the adequated of the adequated

ADVERSE REACTIONS

ABVERSE REACTIONS

Service allowed in instances which may be associated with CopConder* (insponders hydrochonds coprobles-released label the regy in orincal use are those observed, with other opinic advantage, representations, process, registering registers were an exponent process and process

of many cases the frequency of these events busing initiation of the taby may be minimized by writing cases the frequency of teaching dosage, sow physics, and the varietization of large swengs. The platest concernitions of large swengs for the platest adverse events will obtain a case or for the platest adverse events will obtain a case or discussion in interestly at ObjCortio therapy is continued and plates degree of lightwarp is discussed in interestly at ObjCortio therapy is continued and platest degree of lightwarp is discussed.

if clinical traits comparing OxyCorest wat Harmschale-relactic daylocoone and placebo. The most services adverse sweets (> \$1%) reported by patients (\$15) at least once during thirtiesy were:

24014 S	0 cyCor n = 12 # 25 :	17 150	imo Sei	idate- lease 225 is (%)	n n	+45 xs (%)
Constructor Vautes Sonrowice Sonrowice Ocurros Parties Vanning Headone Dry Mosth Actions Switzling Switzling	52 52 52 52 25 27 17 12 13	2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3	58 60 53 33 38 31 79 13	2000年2月日本の日本		の世界の名のの第1名

Doc #: 2415 Filed: 08/15/19 91 of 110. PageID #: 400565
The lottering after its suprimition were reported to Chyclorise troused patients with an industrial between 1% and 5%. It describing occer of frequency triby were subserval, neverousness, instituting, rever confusion, discribe, accommod pain, supposed, as were subserval, neverousfield, deposed, postural hypotherical, childs, historing gestivist, ulmowing because, thought abnormalism, and historial, and historial participations of the confusion of the c

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Himca and Junious Hydrokaropadhy

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Ambados and Namiquesh distyration, edensi, peripheral oderna, thing

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por, carries, trends, window, windown applications

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Sponda Sensor a samerative visits, parti pervision;

Limpersipic dyburs, inertations introdesses polyuria, urinary retention, unhaston limpakesi.

ORIGI ANUSE AND DEPENDENCI (Addiction)
Displaying ** is a mulgarist operative first an abuse fability similar to marganist and it is
Brodest it contracts subdates. Operating instacts an common target for both originations
and only addicts. Debugs at apparent as provided by Carlotters lateful, in believe to neture

The accuse facility of a drug.

Dup addition intriguence receives a systematic by Cayl Option labels, in believed to retrude
the path of the systematic path of the systematic path of the systematic path of the path of the path of the systematic path of

rig pice inflore.

Thysicians should be aware that polychological dependence may set are accompanied by con-current foliations and symptoms of physicial dependence in all addicts, in addition, about all operations can become in the absence of the psychological dependence and is characterized by missage for non-needic authorise, office in combination with other approximation substitution. Occording companies of a dual-polyment material management of the properties and stated from all the tablet constituents, especially tales, can be expected to neguli in local despectacions and purmonary granitames.

OVERGOSAGE

Overmosever.

Acute overdosage with psycodone can be manifested by respiratory depression, somnotence progressing to studor or come, selected muscle facolody, coid and cleaning sice, conspicted pupils, bristycanda, hypotension, and death.

programming to choor or communities, and death inscribing control and claiming series, characteristics, hypothesis or, and death in the historistics, hypothesis or, and death in the historistics and the historistics and

DOSAGE AND ADMINISTRATION

CONTROL PROCESSOR STATEMENT OF THE SWALLOWS WHO SHARE THE APE TO BE SWALLOWS WHOLE, AND AND NOT THE EFFORMS CHIEF TO RESPOND THE PROCESSOR STATEMENT OF CRISISES. THEN SHORE, CHIEF TO RECEIVE THE OFFICE THEN SHORE, CHIEF TO RECEIVE THE OFFICE TO CHIEF THE STATEMENT OF THE STATEM

TION OF A POTENTIALITY TOKIC DOSE OF CONTODONE. In heading part to what is assess the poderer regularly and systematically. Therapy should also benegurary invelored and discissed based upon the superior contributed of part and side effects and the headth profits similar colonic participant.

Only doesn is a managed for the managed test of moderate to assess pain in patients who requires twament with at one code of antigenic for more than a few days. The controlled release entires of the both surface above of the better systematical entery of beautiful Sec CLANCE, PARAMOCOLOGY PHA-SANCOLOGY BASED as properties to the analysis of pagents some pagents may been them asymmetric indifference code given e AM that in PM) docume, some pagents may been them asymmetric indifference code given e AM that in PM) docume, between the pagent pagents and pag

Inhibition of Therapy.

To official to inflate the costing registed for each patient individually training into account the satients prior opicid and two-colonid analyses, treatment, desention should be given by:

(2) the given becomes and individual status of the satient.

(2) the day dosa, possing a wind kind of the satience (s)) the patient has been taking.

(3) the miskably of the overwhele statinate yeard to equal the dose of deposition.

(4) the patient occlorid exposure and opiced patients (s) and (s).

(4) we promise such exposure and upon partners (4) may.

Shift to distinct between cash controls and surverse experiences.

Care shrout be taken to use the initial cross of GryCoron in patterns who are not already opinion to start and expensively from who are receiving controlling the same controls, according to start and expensively from who are receiving controlling to survey design the preciously controlling the preciou

Socialists, of critical services interesting the miscolar plant miscolar, and miscolar, Patheria And Almedy Boog Cooking count density. Chical Trust have shown that patients may intake supple services to time of the foreign with a con-apole strategic floatient of date for most patients who are produced and on the graph of the in-on-apole shall present (MARI) and anotherist later without produced in the continued of the services of the servi

comparements in many or consequent. The devived non-opicial is discontinuous, early upward to the testing of the devived testing of the d

2. Olvide this 24-hour projections does in half to obtain the twice a day (\$12h) does of On/Conto.

OnyCortic.

3 Round down to a dose which it appropriate for the tablet strongths available (10, 20, and 4) mg solved).

4. Organization and other around when-lock opioid drugs when OnyCortic thempy is initiated, this fixed committee and on likely to be substantionly in all patients, especially patients inceiving large opioid coses. The recommended coses shown in Table 3 are only a starting point, and dishe abdensation and finguisht passion are included until patients are stacks on the five finitely.

tasion Factors for Converting the Daily Cose of Prior Coloids to the Daily Jose of Gral

(Mg/Day Prior Opicid x Factor – Mg/Day Oral Ovycadone) Cral Prior Opicid Parentens Prior Opicid

20/C20016		1996
Coceine	0.15	100 Per 100 Per
Fentanyl TTS	SEE BELOW	SEE BELDW
Hydrocodone	0.9	-
Hydromerphera	4	20
Lexophanel	7.5	15
Megendine	2.5	0.4
Mirthadone	1.5	3
Morphice	3.5	1000
"To be a said note for one	A section to cost topy of neuroscient	or madigate managinary block-

we we used may the convention to odd percedone, for adjust sociality, pay-lose previous opiciality, a more content-size opicialism is evaluated. For compile, for high-date parameter is magnitude, and 15 initized of 3 as is multiplication factor. In all coness, supplemental adjusts, the bestook should be made available in the form of imme-diate-release and expressions or wastern suitable short-acting analysis.

TipASI, Conserved from Toxicalermal Pentage to CopConder Eighteen hours totowing the symmal of the final detected formany patch, CbyConten treatment of such conversions, a con-tensive expectage to the conversion of the conversions, a con-servative expectage to the conversion of the conversion of such conversions, and safety for such 25 µg/hr family if transforms patch. The patient should be individed code-ly for such 25 µg/hr family if transforms patch. The patient should be individed code-ly for such 25 µg/hr family if transforms patch. The patient should be observed as

If the rapy distance is there is very limited collected operance with this convenient. Managing Espectral Global Advante Septembers. Note platest enough collects, operably those who also point name, will appriet on selection and managinest in convenient and the selection and managinest in convenient and the selection and managinest platest events such as constitution should be arranged and the said approach to an operation of the selection and the selection of the selection and the selection

Pasianto receiving CryContin may pass an intact matrix "ghost" in the stoor or via cold. These ghosts contain little or no visidual oxycodone and anti-of no clinical consequen-

These ghosts contain the or to vesselus expodent and ent of no otheran consequence. Inhabitatalization of Designe. Once there opinic effects should be transmit; assessed. Present about or the state of the contained of the con

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Table of Appropriate Supplemental Analysis

	grn Resous Dose
DryCordn q12h Date (mg)	immediate-roleage singgodene (md)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×30 mg)	15
50 (2×40 mg)	30
130 (3×45 mg)	30
Maintenance of Therapy	

The intent of the stration period is to establish a patient-specific gifth pase that will maintain adequate analyses what acceptate strategy as the region of the patient strategy and the region of the patient patients. Should be applied the patient patients the rection of the stop adjustment continued to eventually and content. The rection of the stop adjustment continued show allowed the employed in the cartistic pass content. During chance the management of the continued seed for anount—the dock appoint the requirement of the continued seed for anount—the dock appoint the cartistic particularly strough the supportance.

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Cessation of Therapy.

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SAFETY AND HANDLING

earch : and particular (an) Carlos * (an) position hydrosticate controlled-live see) takes are sold design forms that pose no known health mak to nealth-care providers beyond that of any controlled substance. As with all such drugs, care should be sween to prevent oversion or acuse by groper handling.

HOW SUPPLIED

now some controlling of the processor of the symbol OC on one one and 10 on the other. They was used to the follows:

NDC 55011-100-10: endo-resistant clears, gasque plants busines or 100.

NDC 55011-100-10: endo-resistant clears, gasque plants busines or 100.

On/Condir (porocome hydrochroide controlled nisezza) 20 mg tables are mand, unio pre-coloved, content fabrical bearing the symbol CC on one side and 20 on the other are supplied as follows.

NOC 59011-103-10; child-resistant closure, opaque plastic bottles of 100

out prescription.

NOC 59011-1-03-1-2 CPS2-register Colories, opique primo brames in nor Conformation operation and processed and

CAUTION

Manufactured by The PF Laboratories, Inc., Retown, Nu. 07512 Disposes

Distributed by Punkie Pharma L.P. filtrwalk, CT 08850-3590

Copylight© 1995, Purdue Pharma L.P U.S. Pubert Numbers 4,861,596; 4,970,075; and 5,266,531

December 5, 1995 A4909-011

Promotional Ad Slick

NTRODUCING





Small, color-coded tablets (actual size)

Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Item #
10mg 100's bottle	59011-100-10	\$107.16	\$2.00	
20mg 100's bottle	59011-103-10	\$205.10	\$4.00	
40mg 100's bottle	59011-105-10	\$363.91	\$6.00	

^{*}Earn an additional \$3 rebate for stocking two or more different strengths of OxyContin. Maximum rebate allowed is \$15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. No phone orders accepted.

INTRODUCING



Heavy promotional support planned.

- —Promoted by over 300 dedicated professionals—the same sales force that boosted sales of MS Contin® (morphine sulfate controlled-release) Tablets to over \$100 million.*
- —Journal advertising and direct mail to doctors, nurses, pharmacists, hospitals, hospices, and managed care organizations.

Pharmacy Introductory Offer

Receive a stocking rebate on your initial order of OxyContin Tablets purchased during the introductory period: January 1, 1996 to March 29, 1996.

Complete coupon on other side, enclose wholesaler invoice as proof of purchase, and receive rebate directly from Purdue Pharma L.P.

Don't delay! Order your initial supply of OxyContin Tablets today.

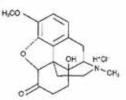
OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

^{*12-}month sales of noninjectable Class II and Class III apioid analgesics through October 1995. IMS Drug Store and Hospital Audit, October 1995.

OxyContin™ 40 mg Tablets (Cxycodone Hydrochloride Controlled-Release)

WARNING: May Be Habit Forming

handware view how Confair - Repositions systematical controlled requires tablets are an opicial paralgebit sup-pilled in 10 mg. 20 mg, and 40 mg tablet strengths for outlindministration. The bodit of investiga-deposite the amount of expressions are submitted as the hydrochlarists and. The structural totals to respect done hydrochlaride is as follows:



Colto-NO. + HO!

MW 351.83

The cremical formula is 4, 5-apoxy-14-hydroxy-3-metroxy-17-ceallythrorsteran-6-one hydrochloide.

hydrochodes. Opposes to a white, odoriess crystaline gowder derived from the occurs allored, treatmen. Opposes in your production distributes in water (1) of 4 to 7 m. s. 1 is startely soluble in allo-red (octantal water carbor coefficient 3.7). The tables contain the following nacrise impair-ents amonotic mellikacytes opposited, hydrocytesyt metrylackidos, lactate, magnesiam therein, positions, not less a coefficient of a trent from the coefficient of the coefficient of addict, intentity yellow that coefficient of the gradual ballet only, and other oppositest.

CLINICAL PHARMACOLOGY

CLINICAL PRARMACOLOGY
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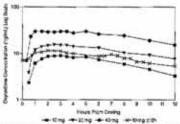
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presortionally has been established for the 16 mg, 20 mg, and 40 mg tacks already offs pask plasma concentrations (C_{rea}) and estent of locuspiton (AUC) uses Tace in the own in the short suff-life of elimination of Doycodons from DoyCordin, steady-state plasme cor

Case: 1:17 md -02804-DAP

OxyContin* To mg Tablets

OxyContin* 20 mg Tablets

OxyContin* 40 mg Tablets

OxyContin* 40 mg Tablets

OxyContin* 40 mg Tablets

OxyContin* 40 mg Tablets

Man /'s coefficient variation/

Congo Form	AUC (10-teseLift	(marrie)	T.	Conc. (rgint)
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15 ray Day Cordin	2073 (45.7)	21.4 (36.6)	21 (57.9)	9.3.
tions Ony Contin	421 [117]	293/34/6	2.1 P7.45	ta.
Author Dose 10 ng DayCartin Nakas g12n	191716	161012	32 (0) 8)	72[481]
i ng isanedake okase adh	arabes.	165 (\$8.4)	11(47)	7.4 (90.0)
Manufacture of the Association of the State	Design of the Co.	45.00		-

Food Effects
To contract to immediate-release formulations, fond has no significant effect on the absorp-tion of propositive from CoyContin. Orycodoral release from CoyContin tables is pri independent.

parmicularist.

Following in Tage materials and instruction, the volume of distribution (Visa) for corporations was 2.60.4g. Corporation binding to extreme protein at 200° and a 5.46 of 7.4 was about 49%. Once accorded on oppositions in distribution to distribution to distribution to distribution to distribution to distributions and format (large accorded to the board on breast mits goes PNECAUTIONS).

Metabolism
Opportunity proprieting in observation in metabolism to reprospostore, organizations, and their placationism. The major circulating emissions is no reproducted with an AUS calls of 0.6 in aller to task of propositions, incorrections in reportunit to be a considerably visible analysis of that expectation. Opportunity, advantage proposed analysis activity is greated in the placement of the propositions. Authority of the proposition of the placement of the proposition of the proposition of the placement of the proposition of the p

The formation of paymer-priors, but not consequence, is mediated by CYP2C6 and as such to formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Experience Dispositions and its irrelationities are encrited primarily via the Malary. The amounts measured is the utilin Nave beam reported as follows: The psycodome up to 19th, conjugated crystodome por to 50% their drywoophome. One our judgment drywoophome is 14th, both mand companies or constructions have been board in the unite of the quantities. The total plasmal extension or constructions have been board in the unite of the quantities. The total plasmal extension or constructions have been board in the unite of the quantities.

businy. The plasma concentrations of on-codure are only nominally affected by age, being 15th greater is alcohy as compared to young subjects. There were no differences in adverse event reposi-ing between young and efterly subjects.

any bosonem young are entropy receptors.

Security Construction of the construction of

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est manual for devications instituted by 2.3 moust given President region. Chapt-drugh statutations (see PSEAN TROMS) — Chapt-drugh statutations on pair via (PSEAN Exception or president institute regional statutation of the fact and statutation of the

CLINICAL TRIALS

CLINICAL TRIALS

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ability of desiracy improved with this stropulation of the characteristic metricy with DupCortins. Use in Centure 1 and a state of the Coulde-blad, controlled clinical trials meriving 3-11 causes patients. Opcortins was state of the 1 and the heading clinical country 10 months. Two, double-blad, controlled clinical studies indicated that 10 pgCortin desired cital his produced analysis of fillions of gellular to the controlled-measure reprocessing stock of 4 days amenited daily double his and trough plants controlled-blad statistics of the 1 and those adjaced with memory double-measure procedure as described in the Country of others. After this statistic to assigned with memory and the controlled that the controlled of the country of the country of the Depoint.

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in gatestia with cancer pass, the total daily DayContin does technic ranged from 20 mg to 640 mg por day. The average total daily does was approximately 106 mg per day.

my por day. The average both daily does was approximately 105 mg per day. Source in stage Chancer hale. A challed large provides provide group may visc conducted in 135 patterns with moderate in severe observations pairs, who every elogical strategy before pairs pairs content with moderate is severe observations pairs, who every elogical strategy before pairs content with moderate in patterns and a consideration of the safety participation of the patterns and the safety participation of the content and concentration—elect relationships were model with a minimum effective glasses and appropriate to group participation of appropriately 5–10 agrees. In a double-olived, active controlled on consideration of appropriately 5–10 agrees. In a double-olived, active controlled with one controlled value or position and project framework by Cyclothia administration of 15th participation and p

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DeyGortist gave requirement poets exclusive effect commands to two psycholdres 5 mg (acetamicropher) 25m grades and of 15 mg immerciate-release expressions, who is to 90 mg does or
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esticitizated. Other Citical Plats.

The Children Plats involving approximately 200 patients with calcular-stated and non-cancer in open-stated this shoulding to the cackage releff recommendations, appropriate analysis effectiveness with moter without region to age, peticle race, or disease state. There were no oricitated drug-interactions outcomed in patients recoiving a wide range of medications common in these applications.

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INDICATIONS AND USAGE

indications and graves.

Optication in billing are a controlled-release and formulation of enjococone hydrochories and cated for the management of moderate to severe pain where use of an opicial shotopic is appropriate for more than a few risys, (See: CLIRICAL PHARMACOULD'S; CLIRICAL TRAILS).

CONTRAINMENTATIONS

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WARRINGS
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GE CRUSHED Conflowed TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DODGE OF CONTROCHE.

TION OF A POTESTIMALY TROOG DOSE OF COYCOGONE.

Respiratory propression:

Respiratory propression is the chief is used from all codes appoint, preparations. Respiratory expression occurs medit sequently in easily or calculating preparation, usually selectivity larger has doses to non-foliativity proteins, or when opposits are given in conjunction with other agents that depression around be used with extreme causion in calculat with significant, chronic obstructive personancy decision on or primorate, and in patients having a substantially decreased respiratory referred, hisposis, type-prosping, personalizing resources that the protein of the p

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PRECAUTIONS

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Research, and the Athefician Pain Society. ther of Orychosth is revokable with accessed potential case and should be used only with caution in the Selving conditions: access also beliefs; adverso contact insufficiency or git. Addison's debase! (Diff organisation or communication in sharing obtilized patients, signocount select accessed with respiratory objects; or communication or highly objects propriet productions.

psycholes.
The administration of coprositine, like all opicid revigences, may obscure the disapposition of chieful course in patients with actual abdominal conditions. Overcooper may appreciate conversions in patients with convenience and all opicids may induce or appreciate solutions in some chieful settings.

Interactions with other IDE Depressants
Copyority, the air considerations about the conditions with other in an educated course (in the air consideration with other patients) and souther control of the cause description, should be used with courters may control in a reduced disapper (in to the cause description, in software the services of the course of the control operations of the course of the control operations of the control operations of the control operations of the course of the control operations with the several disease of CopyCostin.

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issace. Protects who are already receiving CopComfor tablets are part of origining an algebra therapy may be study continued on the drug if appropriate distrige edystriments are much considering the procedure, other charge gives and the temporary changes in physiotopy caused by the servi-cular intervention (see PRECAUTIONS) thrug-Drug Interventions, and ODSAGE AND ADMINISTRACTION. (be in Parametic/Bislary Peol Disease

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brandle: Export (see 2005/6E AND AQMARETRATION Clearation of Therapy). Information for Preferent/Carpholorum (long/Costin International Projection) of the complete and the complete of the cost of t

Patients should be advised not to adjust the dose of DayCortin without consulting the pre-scribing professional.

CONFIDENTIAL

Case: 1:17-md-02804-DAP

4. Palants stroug at a sold and the first strong at a sold and the first strong at a sold at a popular sold at a sol

because additive checks may occur.

If Women of chickbearing optimitis with become, or are planning to become, program should be advised to need their physician regarding the affects of amilipation and other drug use ording programs or internetwes and their drug use of their physicians. Planning the drug of their programs, the program of their physicians of the drug of their physicians of their physicia

Projects should be addused that they may been empty matrix 'ghosts' (tallers) via pro-ny or in the check, and that this is of no concern since the address medicables has al-been absorbed.

(ay) or in the proce, me consistent of the process of the process

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Preplacacy Freedpoint Ethiotis — Category R. Reproduction statism have been performed in rata and cat-bot by and administration of doses up to 5 amples (45 mg/km) and 125 mg/km (1375 mg/km) responsibly. These doses in an indication as a fundamental of 125 mg/km (1375 mg/km), the complete of 20 Mg and (17 and 15 americs the hands dose the last open mg/km). The results of consistent of 20 Mg and (17 and 15 americs the hands dose there are received in a doses and administration of the mg/km (18 americs). Source a serial representation disclosed and the production of the mg/km (18 america) because a serial representation disclosed to the production of the mg/km (18 america) and the serial disclosed if Category research.

Notice requires the Check — Nationalities whose mothers have been halling onlycopping chronically many call fail respiratory degrees on and/or withdrawal symptoms, either at both ancion in the nursely.

nations, Labor and DeSkey CayCodinis and recommended for use in women outing and immediately prior to labor and colored because one opinion may cause inspiratory depretation in the tereform. Anyting Stateme one opinion may be been selected in creat milk. (Microswe synctrom can occur in breat-hosting informs when materials desirishadion of an opicid analysis of seapon. Ordinarily, reasons should not be undertaken while a potent is receiving DryContin labor despectation may be exceeded in the mak.

Production Use Codings and effectivements in production patients below the pay of 18 have not been established softly that distings from all propositions. Nowever, opposition that been state commonly in establish populations in other charges ferms, as have the exclusive seen of the farm below. No expected increases discrete expected from the use of their terms of expected on the farm below. No expected increases discrete expected from the use of their terms of expectations in obtaining and an except to supply use to be a supply of the payon of the payo

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Disapper should be appured according to the present years on Sender Ofference and sender of the present that the demonstrate sport to 25% higher everage in pital microbination studies, opinio-raise fermatics demonstrate sport 25% higher everage plants conventioned and percent impranting of typical opiniod advance events tituut makes, even after adjustment for body weight. The district relevance of all ofference of this magnitude is one for a drug broaded for compile sport or including an including of discours, and there was no make female ofference colocitud for efficiency or adverse events in constall trafs.

ADVERSE REACTIONS

ADVERSE REACTIONS
Certain adverse verbille may be appointed with DeyDurder* (serpospone hydrocenetic controlled-masse) such at his ray in circ data use an itions observed with other speed appeals, including secretary array, and in an even feater depend appeals, including secretary array, and in an even feater depend containsy depression, importancial or inhall (see SVERDOSS). The one-lensing selection and in a popular soon or inhall (see SVERDOSS). The one-lensing selection and selection and selection of the se

where yether gives activated. In things case of the departs during initial on of the acy may be in in mayor by careful influences of the acy may be in in mayor by careful influences of the acy careful influences of the processor of the acy of th

in distributional comparing De/Contin with immediate release devications and public, the most common soveres events (>5%) reported by patients (ph.) at least once during the any were:

Table 2 **CvyCortin** Raceto Release n=227 多數係 多的作 # pts (%) Constitution Names Semigrates Districts **通知教教教教育性有限 通行程度行任司任任务** 89988953 動物物物物の対対 四四四日四日の東京の Prunter Vonting Heastone Dry Mouth Authoris

There are Comprate tymphadenopathy Mitolock and Number thinydraton citims, periphera sciena, trest

American and Administration configuration counts, perspects security, treats in futured in American depote particular, in a control of the configuration of

BRIGG ARANG AND GEFENDENCE (Addition)
Conforms " is a multipoint opinion being an assess labbig similar to enophine and is a
Schedule Controlled statemen Opinion projection in common largests for both drug abuses
and only addition. Deliging absorption, as provided by Ony Contin states, is believed to reduce
the above faults for its drug.

and orang authoriti. Conjugate absorption, as propulated by disposition transmits in animated to require a share abusing of an image. Drug addition image dependency and abuse of orang for his intermediated by a processipation of the statistic many dependency and abuse of orang for his intermediated by a processipation of the statistic many dependency in the statistic many dependency in the statistic many dependency or an intermediate of the property of the statistic many dependency or an intermediate of the statistic many dependency or an intermediate of the statistic many dependency in the statistic many dependency or an intermediate of the processing of the statistic many dependency or an intermediate of the processing or an intermediate of the processing of the statistic many dependency or an intermediate of the processing of the processing or an intermediate of the processing of the processing or an intermediate of the processing of the processing or an intermediate o

DVERDOSAGE

OVERDOSAGE

Acute compromes with expectations can be mainlested by explicatory depression, sommotions experienced by expressions of support of come, sweets masche flactodate, cold and daming size, consisted publis, bredynards, hypotensice, and death is the seasoned of supposition expenditures, and death is the seasoned of supposition expenditures of a potential many and important on accordance or committee verification. Supporter many discharge pages and versportances pillabels to maniphoral not expressions of control products and pathonary appears and versportances pillabels to maniphoral not expressions of control products and pathonary expensions of ordifications. The pure opicial antengonaries such as malaries or ordifications are projected antengonaries such as the accordance of controls of support of controls or ordifications are projected antengonaries such as the accordance of controls of support or ordinary ordinary ordinaries of from discharged and accordance of controls of support ordinary ordinaries of the accordance of controls of support ordinaries of the accordance of controls of support ordinaries of the accordance or ordinaries of the accordance of controls of support ordinaries of the accordance or ordinaries or ordinaries or ordinaries or ordinaries or ordinaries ordinaries. The pathonary ordinaries ordinaries organized ordinaries or ordinaries or ordinaries or ordinaries ordinaries organized ordinaries ordinaries. Present acts or prescribing information for

DOSAGE AND ADMINISTRATION

Garante Principles
OngCaster** (organismos hydrochlaride continued-release) TABLETS ARE TO BE SWALLOWED
WHYDLE, AND AR HOTT OILS SPICIALLY, CHEWED ON CHARGED, TAKING SPROCK, DIEWED
OR CRUSHED DONCCHIEF TABLETS COLED LEAD TO THE RAYD RELEASE AND ABSORPTHON OF A POTENTIALLY TAXING COORS OF ENTIRODNE.
In Insulang pain it is waith a sesses the patient requiring and systematically. Though should be
on applicate primeries of the continued based count for patients own imports of pass and size division
on the health professionants claims profess.

(Application is branded for the amangement of amortime to be every the pass in the state of the remarked of the state of the formation allowed to be of the control of the state of the size of the state of the size of the state of the size of the size

Terristy

It is critical to inflore the desire regimen for each pottern individually, taking into account the patients profession and one-dood analysis between individually, taking into account the patient profession and testing a state of the patient

(3) the day door, power, and used of the analysis state of the patient

(3) the day door, power, and used of the analysis state of the patient

(4) the patients opials supersure and other analysis to accessing the store of exposione

(4) the patients opials supersure and other themselve (if any)

(4) The platform opiots approximate and opiots following in the properties of the platform opiots approximate and authorize propriement. One of the other platform on the interest of the platform opiots o

us being provided. It may be continued in the purious non-optical in decentiment, early expected object trades may be interested. Part of the continued of the

Uniqueness 23. Round down to a dose which is reported and for the tablet strengths available (10, 20, and 40 mg tables).

40 mg tablets).

4. Discourting all other area and the clock opicid only a when CovyContin thereigh is find that the convergence and is finally to be autofactory in all patients, exceedably ballings receiving topic opicid closes. The recummanded codes shown in Table 3 are only a starting goals, and close observation and trappart litration are indicated antil patients are stable on the new therapy.

Tabbe 5

Multiplication Rectors for Conventing the Daily Dose of Prior Coincids to the Daily Dose of Gral

(Mg/Day Frior Opiole's Factorie Mg/Day Drai Oxycodune) Drai Pitor Opiole Purenteral Prior Coloid Chycodore Codelne 0.16 Codeline Fertanyl TTS Hydrocodone Hydrocodone Leverphanol Meperidine Mathecone GRE BELOW SEE BELOW 20 15 0,4

Acquire.

To be used only for conversion to one doycodone. For pallants receiving high-dose parenteral
opicists, a more conservative conversions is warranted. For example, for high-dose parenteral
of morphise, use 1.5 tested of 3 at a newlip leason faster.

our morphone. Libe 1.5 interess of a ALS is making eapport states.

Ye all cases, suportemental are gester (see below) should be made exalibite to the form of immediate-release on a long-codone or aporther suitable short-coding analysis.

by the carty tradeor at times is very shaded clinical experience with this convertion. Averaging Separated Copiest Average Experience is a selected stake, will experience side other. Most patients monthing opticity, according the basis optical stake, will experience side others frequently the side offereds from Copiests are basis, but may receiv execution and management. Adverse exerts assumes constitution should be articulated and typical and the stated apprecisively once proportionability with a stamplate should be articulated and treated as the considerated of effects such as sentiation and number of successful should be appreciated as the other should be appreciated as the considerated side effects such as sentiation and number as usuaday self-initiate and other does not person beyond the first flew why. If a success operation and is uneconstable to the operand, manned with eith-emistics or other mode likes may release these symptoms and should be con-sidered.

Riderts receiving DeyCortin may pass an intext matrix "gnost" in the stool or via neitor. Thisse gnosts contain little or no residual crystochore and are of no clinical consequence.

This is greate coming the or no residual commonne and are of no district consequence, immediately of consequence, and other opicial effects should be frequently associated. Protests alread to this service, just noted and other opicial effects should be frequently associated. Protests alread to this service, and include a service of consequence of the protect of the property as of the consequence of the protect of the pr

to 50% of the current does at each increase. If again of receipting option of the desired objects are obtained, the next does may be received if this education is lead to inside, each supplemental does of increase development is lead to inside part attention of the adjustment leads to inside option on the inside objects or may be given. Alternatively, in one-object camping a dispurious development is worked, beat adjustments should be made to coasia an appropriate between pain resid and project-indeed adjustment options for the therapead option of mild or not pain is activated. The events therefore a formed a option of the several therapead option of the several therapead option of the coasial and option option of or changing an allegative requirements, including leads that then, the operand coasial is recommended between physician, other members of the residuction to.

the caregivas to

is recommended to the caregiver family. Supplies around the cook the large with controlled release opinion will need to have arrested upon a recommended to have arrested to have arrested to the arrested to

Table of Aportorials Supplemental Analysis

	prit Resour Dos
On/Cooks of 2h Dose (mg)	physocone (mg
10 (1×10 mg)	5
20 (Z×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (2×20 mg)	15
50 (2×40 mg)	20
120 (2×40 mg)	30
Africationnois of Thursday	

Abbitismence of Therapy. The listent of the Britiship period is to establish a patient-specific of 2h does that will maintain adequate analogists with ecopyrable side effects for as long as pain resile in recoverant. Should pain recur their to be not be convenedrably involved to we spatial pain control. The technol of thorapy adjustment outlands show should be employed to re-establish pain custors. During chronic through especially for thorseless pain systemates. The continued most for allowing feet book apposit through should be instantiated periodicities (e.g., every 6 to 12 months) as open-fied book apposit through should be instantiated periodicities (e.g., every 6 to 12 months) as open-

protes.
Cassacion of Therapy
When the patient in Anger requires therapy with DigCost in tablets, patients recribing drags
of 23–20 ergistry det issuely leave the terropy sopped absorpts, without histories in the terropy sopped absorpts, without histories in the terropy and patient of application of introduced in the patient leaves and application of introduced by a few patients and introduced by 25% every and interest by a patient substitution of the telescopy and interest and the state of the analysis and every application of obtaind makes talkents (10 or 20 mg citities. Therapy call
was the disconstruent.

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conversions notify logication of Proteins of Operation.

To should overlook, conversitive dose conversion radius should be followed. Initiate involvement with about 50th of the estimated op, analysis deep dose of passing in expedication can be sub-vide instructive doses broard on the appropriate dosing internal, and librate lazered upon the patient's

SAFETY AND HANDLING

Cos Codin ** I avo constature.

Cos Codin ** I avo codons fly dischloride controlled-educate ballens are cold coace forms that
pade not make bealth risk to breath-case proviours beyond that of any coacealed auctitance.

As with all such drugs, care shorled be taken to provent diversion or deuse by proper handing.

HOW SUPPLIED

HOW SUPPLIED.

(CopCortin ** improcorde hydrocrifotice controlled-release) 10 mg tablems are round, shecowed, write-doored, contress tabless bearing the symbol OC on one sitils and 10 on the other They are a upplied to finitioner.

NGC 99011-100-10, claim-released indicates apeque plassor bottler of 100 mg of the other controlled on the controlled or symbol OC on the site and 20 on the other they are controlled or symbol OC on the site and 20 on the other they are applied at the titlewin.

plant-obtained, convention common common parties are supplied as follows: MCC 55011-1001-10: mbd-cestitated obsques, opegate plastic borders of 100 Opcoartie (composate hypotrolishinde contectied-release): 40 mm; statety, see count, whitever, yellow-calders, common ballets bearing the symbol OC chi one side and 40 on the other. They are supplied as follows:

NDC 59011-965-10: cn86-militant deems, opaque platitic botika of 100 Sone tades at controlled room temperature 15-20°C (66-66°F) Dispense in 1ght, light-resistant container

CAUTION DEA Order Form Required. Federal law problems dispens

ing without prescription. Manufactured by The FF Laboratories, Inc. Tolonia, R.J. 07512 Distributed by Purdue Pharma L.P. Norwalk, CT 06850-3590

Copyright© 1995, Purpue Praema L.P. U.S. Patent Numbers 4,861,596; 4,970,975; and 5,266,351.

A4909-811

Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 96 of 110. PageID #: 400570



Small, color-coded tablets (actual size)



Strength/Quantity	NDC Number	AWP (100 tablet bottle)	Rebate (per bottle)*	Wholesaler Item #
10mg 100's bottle	59011-100-10	\$107.16	\$2.00	
20mg 100's bottle	59011-103-10	\$205.10	\$4.00	
40mg 100's bottle	59011-105-10	\$363.91	\$6.00	

^{*}Earn an additional \$3 rebate for stocking two or more different strengths of OxyContin. Maximum rebate is \$15 per pharmacy location. This offer not to be combined with any other promotional offer.

Order your initial stock of OxyContin Tablets now. Only orders accompanied by a DEA 222-C form will be processed. No phone orders accepted.

Introductory Offer For Pharmacies Promotional Period: January 1,1996 to March 29,1996. Earn a stocking rebate on your initial order of OxyContin Tablets. Store Name Date Address City State Pharmacist's Signature

To receive your rebate, submit a copy of the wholesaler invoice showing your purchase of OxyContin Tablets during the introductory period (January 1,1996 to March 29,1996). Mail to Purdue Rebate offer, P.O. Box 81771, Chicago, IL 60681-0771. This form must be sent with wholesaler invoice. No forms accepted after May 1, 1996. Please allow 4 to 6 weeks for delivery of your check.

MS Canfin is a registered trademark of The Purdue Frederick Company.

Please see full prescribing information on inside pages.

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A4916#SS 000POB

PUR 33061

For patients with moderate to severe pain requiring opioid therapy for more than a few days.



Q12h OXYCODONE HCI CONTROLLED-RELEASE) TABLETS Warning—May be habit forming

The analgesic efficacy of immediate-release oxycodone. The ease of q12h dosing.

Steady-state blood levels achieved within 24-36 hours allows titration every 1 to 2 days, if necessary

No "ceiling" to analgesic efficacy may be titrated upward when clinically necessary

In a multicenter clinical study...

 Titration enhanced efficacy of therapy only 3.5% of patients discontinued due to inadequate pain control when allowed to titrate and use rescue medication

OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The most serious risk associated with opioids, including OxyContin, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and weakness.

*Data on file, Purdue Pharma L.P.

OxyContin Titration Guide

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

	OxyContin Tablets q12h dose	Immediate-Release (IR) Oxycodone dose for rescue [†]	
_	10 mg q 12h	5 mg	
10mg	20 mg q 12 h	5 mg	Titrate the OxyContin
	30 mg q 12h	10 mg	dose if more
9	40 ng q 12h	10 mg	than two
20 mg	60 mg q 2h	15 mg	per day are
0[80 mg q12h	20 mg	needed.
40mg	120 mg q 12 h	30 mg	

Titrate patients every 1 to 2 days, if necessary.

Increase the dose by 25% to 50%, if necessary; do not increase the dosing frequency.

Manage breakthrough pain with R oxycodone' at V₄ to V₃ of the 12-hour OxyContin dose."

E levate the OxyContin dose if more than two rescue doses are required per day.

*For patients taking OxyContin 10 mg q12h:

- The next titration step should be 20 mg q12h

- Breakthrough pain should be managed with IR axycodone 5 mg

^{*}See professional prescribing information for immediate-release axycodorie.



Small, color-coded tablets (actual size)

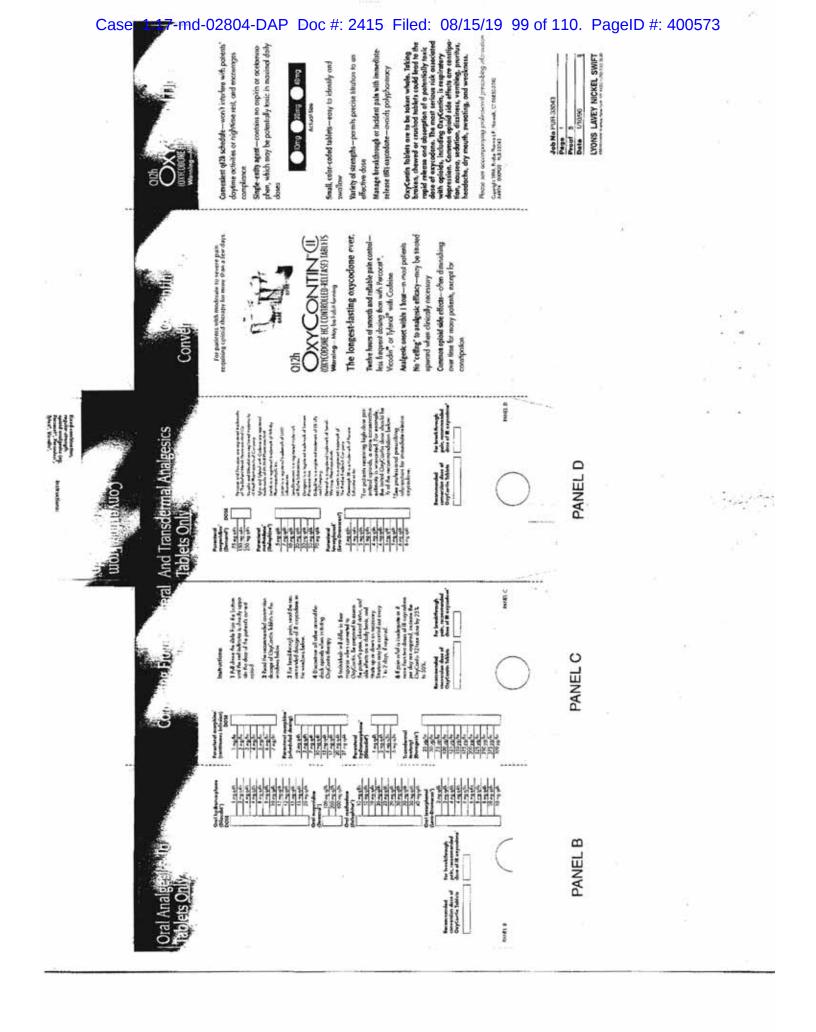
OXYCONTIN®

(0XYCODONE HC! CONTROLLED-RELEASE) TABLETS

Warning—May be habit forming

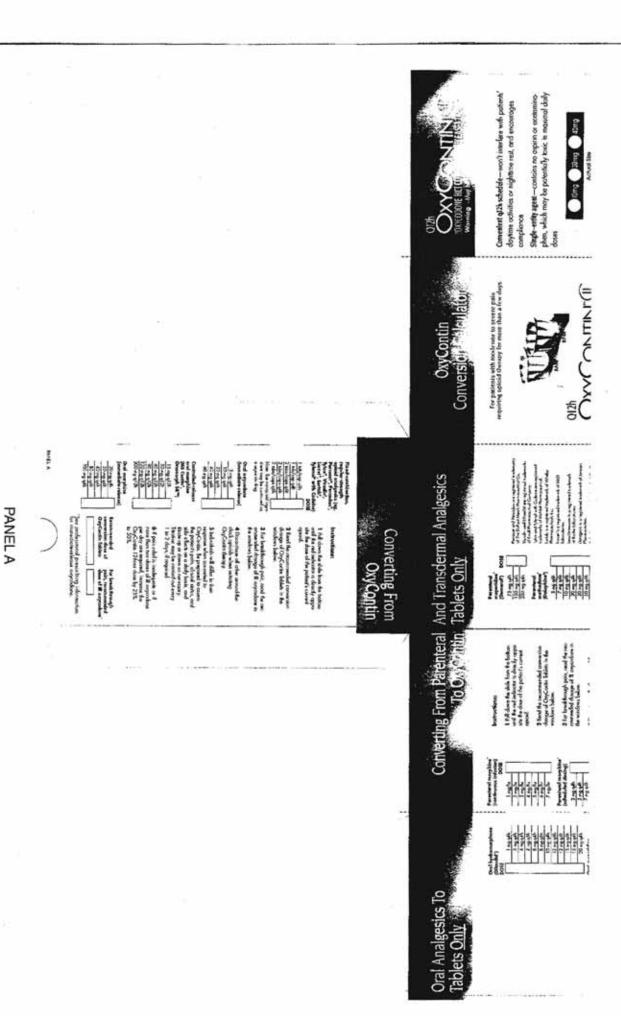
Please see accompanying professional prescribing information.

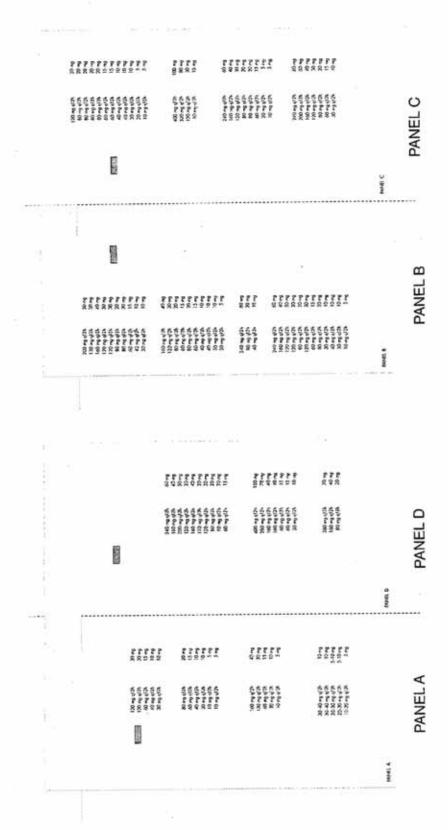
Copyright 1995, Purble Thorma L.P., Norwalk, CT 06850-3590 A4898 000POS Rulk-33054

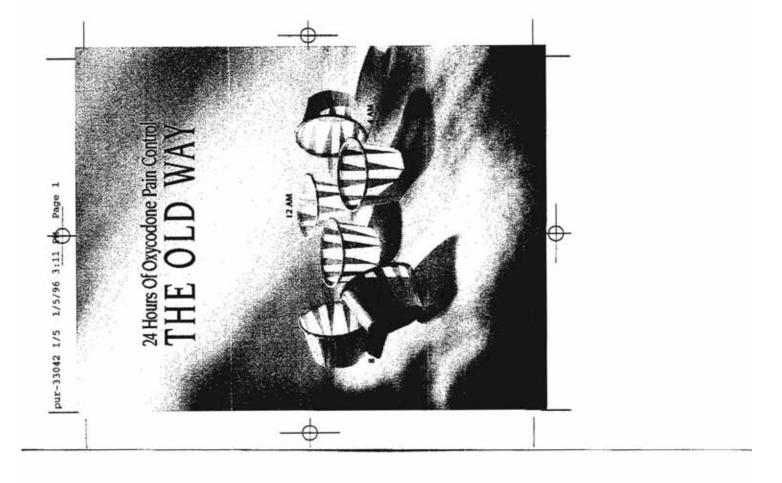


CONFIDENTIAL

**P0629000-IHDand Case: 1:17-md-02804-DAP Doc #: 2415 Filed: 08/15/19 100 of 110. PageID #: 400574







For patients with moderate to severe pain requiring opioid therapy for more than a few days.

Warning May be habit forming Introducing New q12h

The analgesic efficacy of immediate-release oxycodone The ease of q12h dosing

Twelve hours of smooth and reliable pain control—less frequent dosing thon with Percocet*, Vicodin*, or Iylanol* with Codeine

Analgesic onset within I hour -in most potients

Single-eatity agent—contains no capinin or ocetominophen which may be potential toxic in maximal daily doses

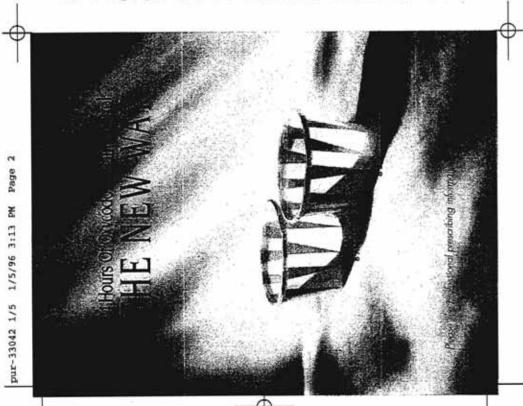
No "celling" to analgesic efficacy—may be shated upward when clinically necessary Common opioid side effects—often diminishing over time for many potients, except for constipation

pruritus, headache, dry mouth, sweating, and weakn

Percoot is a registered trademark of The DuPort Merck Pharmaceutical Co. Vicadin is a registered trademark of Knall Pharmaceutical Company. Sylenal with Codeine is a registered trademark of McNall Pharmaccutical.

OxyContin

The longest-lasting oxycodone ever.



PURCHI-000623087

pur-33042 1/5 1/5/96 3:16 PM Page 4

spends with medicate to severe pain requiring optical therapy for note than a for days

)xvContin

The logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids:

Add to or replace nonopioid with OxyContin.



Adapted from Memogenest of Concer Plain Chrisci Produc Guidellee No. 9. Boduille, Md. US. Day of Houlle and Harren Services AMON poblication 94-0592. Buble: Health Service, Agency for Health Care Pubry and Research; March 1994.

O12h OxyContin— ideal for initial around-the-clock (A-T-C) opioid therapy.

THE ONE TO START WITH (A-T-C).

Iwelve hours of smooth and reliable pain control—less frequent
dosting than with short-acting products such as Percoces."
Percoden, Tylox, Vicodin, Larlab, Lorcel, and Tylenol with
Codeine

Oxycodone is the opioid ingredient in Percocet, Percodan, and Tylox

- Patients are spared the added potential toxicities of maximal daily doses of ASA or APAP
 - Convenient q2h schedule won't interfere with patients' daytime activities or nighttime rest, and encourages compliance
 - Potients are less likely to anxiously "clock watch" when pain is controlled over long periods

Percadan is a registered trademark of The DuParia Merck Flormocourtical Co. Vyox is a registered trademark of McNeil Pharmacourtical, Lortob is a registered trademark of Whitby Pharmacourticals inc. Loreer is a registered trademark of UAD taboratories.



Please see professional prescribing information on last pages.

PURCHI-000623088

CONFIDENTIAL

9 Page pur-33042 1/5 1/5/96 3:22 PM or calconis with moderate to secure cain requiring appoint therapy for more than a fert days

Analgesic onset within 1 hour in most patients.

Analgesic onset within 1 hour plus a longer duration of action than Percoost, Vicadin, or Tylenal with Cadeine

Percent of patients experiencing analgesic onset.



From a single-dose study.

Sunshine A. Orsei, peak, and duration of analyseic effect using the sorting technique: a comparison of controlled-release oxycodone v. immediate release oxycodone alone and in combination with acetaminophen. American Pain Society Program Book: 1994; A-36,

Please see prafessional prescribing information on last pages.

PURCHI-000623089

OxyContin clinically studied in various pain

- More than 10 clinical trials
- More than 700 patients with either cancer or noncancer pain
 - 100% of patients receiving OxyContin were dosed q12h

In a placebo-controlled, fixed-dose tria

- in 133 osteoarthritis patients'...
- Prompt reduction in pain intensity occurred within the first 24 hours By Day 3, patients had achieved 94% of their total pain reduction
 - In this study, OxyContin 20 mg q12h.
 - Significantly decreased poin
- 100% of OxyContin patients were dozed q12h - Improved quality of life, mood and sleep

(CR) oxycodone on pain inhensity and activities in patients with pain secondary to asteoarthritis. Presented at the American Pain Society, November, 1995, Los Angeles, CA. Patients entering the study on NSAIDs remained on them throughout the trial. t Roth S, Burch F, Fleischmann R, et al. The effect of controlled-release



THE ONE TO START WITH (A-T-C)

The one to start with [A-T-C]

CONFIDENTIAL

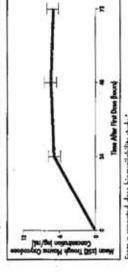
œ Page 1/5/96 3:33 PM pur-33042 1/5 For provious with moderate to severe pain requiring option therapy for more than a fee days

OxyContin

Easy to titrate:

In cancer studies

Steady-state blood levels achieved in 24-36 hours.



From a repeated-dose bioavailability study.

No ceiling to analgesic efficacy.

 OxyContin can be titrated upward when clinically necessary With full againsts, such as expendance, "effectiveness with increasing doses is not limited by a 'ceiling."

† Management of Cancer Pain: Adults. Citnical Practice Guideline. Guick Reference Guide for Clinicians. Rockvillo, Md: US Dept of Health and Human Services AHCPR publication 94-0593. Public Health Service, Agency for Health Care Policy and Research; March 1994.

COXYCODONE HCI CONTROLLED RELEASED TABLETS Marning May be habit forming New qi2h

Rease see professional prescribing information on last pages.

THE ONE TO STAY WITH.

 Titration enhanced efficacy of therapy—only 3.5% of concerpolients discontinued (due to inadequate pain control) when allowed to titrate and use rescue medication - Patients were thrated as quickly and easily with OxyContin

- 92% of potients were fitrated to stable poin control with as with immediate-release oxycodone

The one to stay with

- Average time to stable pain control was 2 days 100% of OxyContin patients were dozed q12h OxyConfin

Roder R, Kaiko R, Grandy R, et al. Steady-state bicorrailability comparison of controlled release oxycodone [OxyConfin] tablets vs. oxycodone and liquid. American Pain Society Program Book. 1994; A:36, #94604 (Abstract).

PURCHI-000623090

Page 10 pur-33042 1/5 1/5/96 3:41 PM attents with moderate to secure man requiring opioid the app for more than a feet stays

Common opioid side effects...

Hents (n=86).	Week 10
by cancer po	Week 5
reported over time	Week 1
Adverse experiences reported over time by cancer patients (n=86	Parameter Anna

Drug-related ADE	Week 1	Week 5	Week 10
Nousea	20	12	4
Sedation	14	80	80
Dry Mouth	٥	0	0
Vomiting	8	7	0
Pruritus	7	0	0
Dizziness	9	S	0

*Percent of patients reporting ADE once or more during specified week of OxyConfin therapy.

Many diminish over time, except for

EASY TO LIVE WITH.

constipation.

- The most serious risk associated with opioids is respiratory depression
 - A significant decrease in the percent of patients reporting adverse events was seen between the first and last weeks of the study (P<0.0001)
- Most side effects diminished over time, except for constipation, even as daily doses increased
- Common opioid side effects are constipation, nousea, sedation, dizziness, vomiling, pruritus, headoche, dry mouth, sweating, and weakness

Kaplon R, Parris W, Croghon M, et al. Decrease in optaid-related advanse experiences (AE) during chronic therapy with controlled-release oxycodones (OxyCR) in cancer pain patients. Presented at the American Pain Society, November, 1995, Los Avgales, CA.

Easy to live with



Please see professional prescribing information on last pages.

PURCHI-000623091

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For particular with moderate to see eer poin requiring optical therapy, for more than a time days.

OxyvContin

EASY TO DOSE.

Starting on OxyContin.

Recommended initial dose for opioid-naive patients.

For supplemental analgesia:	Immediate-Re
For around-the-clock pain:	

	and a second
OxyContin"CII	Immediate-Release (IR) Oxycodone
10 mg q12h If a nonopioid analgesic is being taken, it may be continued.	5 mg administered 1 hour before anticipated incident pain 5 mg administered
Worning: Respirotory depression occurs most frequently in elderly.	for breakthrough pain (if needed)

Wernings Respirotory depression occurs and frequently in elderly, debilitated poliests, usually following large tailed doses in non-holeront poliests, or when opioids one gives in conjunction with other or against that depress respiration. See WARNINGS and PRECAUTIONS Sections in professional prescribing

Note: If more than two rescue doses one needed per day, OxyContin should be titrated upwurd.

See professional prescribing information for immediate-referse oxycodone.
 Please see professional prescribing information on lost pages.

Converting to OxyContin.

Dose of regular-strength Recommends products (eg. Percodons, OxyContin Myox', Vicadin', Lortab', Lorcel', conversion and Tylenal' with Cadeine) range	Recommended Oxycontin conversion dose range	IR exycodone rescue dose for breekthroug pain
1-5 Toblets/Copsules/ Coplets per day	10-20 mg q12h	5 mg
6-9 Inblets/Capsules/ Caplets per day	20-30 mg q12h	5-10 mg
10-12 Toblets/Copsudes/ Coplets per day	30-40 ng q12h	10 mg

Note: The nonopoloid ingredient may be continued as a separate drug. Discontinue all other around-the-clock opicies when initiating OxyContin therapy.



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moreover with moderate to service pain requiring episod therapy for gone that $z \approx d_{\rm C}$.

OxyContin

EASY TO DOSE.

The goal of titration:

To effectively control pain with two or fewer rescue doses per day.

OxyConfin Tifration Guide

IR oxycodone dose for rescue	5mg	5mg	10 mg OxyConfin dose	Transfer of more than tw	de con little de la constant de la c	20 mg	
OxyConfin Tablets q12h dose	10 mg q12h	20 mg q12h	30 mg q12h	20 made	医型和胸侧形	80 mg q12h.	
	Omn			(B)		0	

*See professional prescribing information for immediate release asycodone

I itrate patients every 1-2 days, if necessary.
I ncrease the dose by 25%-50%, if necessary[†]; do not increase the dosing frequency.

Manage breakthrough pain with iR oxycodone" at ½ to ½ of the 12-hour OxyContin dose!

E levate the OxyContin dose if more than two rescue doses are required per day.

For patients taking OxyContin 10mg q12h...

The next litration step should be 20mg q12h

Breakthrough pain should be managed with
IR oxycodone 5mg

New qizin OXYCOONTIIN"(II) (0XYCOONE HC CONTROLLED-RELEASE) TABLETS Warming — May be lookel forming

Easy to dose

Please see professional prescribing information on last pages.

PURCHI-000623093



The one to start with (A-T-C).

The one to stay with. Easy to live with.

Easy to dose.



10mg 🕮 20mg 💮 40mg

Small, color-coded tablets (actual size)

The longest-lasting oxycodone ever. OxyContin

*Around-the-clock.

Please see professional prescribing information on preceding pages.

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